Evidence-based Management in Autosomal Dominant Polycystic Kidney Disease

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Zusammenfassung

Die autosomal dominante polyzystische Nierenerkrankung (ADPKD) ist die häufigste monogen vererbbare Nierenerkrankung und etwa 50% der betroffenen Patienten werden zwischen dem 50. und 60. Lebensjahr nierenersatzpflichtig. Ein zentrales Therapieziel ist die Verlangsamung der Krankheitsprogression, wofür einerseits die Krankheitsprogression prognostiziert werden und anderseits entsprechende Massnahmen für das ADPKD Management getroffen werden müssen. Im Jahr 2016 wurde das erste Medikament Tolvaptan zur Verlangsamung der Krankheitsprogression für einen schweren Verlauf zugelassen (Schweiz). Bis dahin konnten nur Begleiterkrankungen behandelt werden und daher waren Anpassungen des Lebensstils umso wichtiger für das ADPKD Management. Diese Dissertation beinhaltet drei Studien, welche zu einem evidenzbasierten ADPKD-Management beitragen. In der ersten Studie wurde der kausale Zusammenhang zwischen Kaffeekonsum und der Krankheitsprogression in der Schweizer ADPKD Kohorte untersucht. Die unaufhaltsame Progression von ADPKD hat viele Ärzte dazu veranlasst, eine Reduzierung von Risikofaktoren wie dem Kaffeekonsum zu empfehlen, dies trotz fehlender klinisch-epidemiologischer Studien. Die Ergebnisse unserer Studie, welche die erste longitudinale Studie überhaupt ist, zeigten eine bessere Nierenfunktion und einen leicht milderen Abfall der Nierenfunktion bei ADPKD Patienten mit Kaffeekonsum im Vergleich zu ADPKD Patienten ohne Kaffeekonsum. Demnach bestätigen unsere Ergebnisse die *in vitro* Ergebnisse nicht, dass Kaffee ein Risikofaktor für einen schweren ADPKD Verlauf ist. In der zweiten Studie war es das Ziel, einen Triage Test zu entwickeln, der Patienten identifiziert, die noch unterhalb des Nierenvolumens liegen, welches zur Verschreibung des Medikaments Tolvaptan notwendig ist und damit unnötige MRTs vermieden werden können. Diese Studie adressiert die Herausforderung im ADPKD Management, dass derzeit bei allen Patienten eine Messung des totalen Nierenvolumens (TKV) mit Magnetresonanzbildgebung (MRT) durchgeführt werden müsste, um die Indikation für eine Therapie mit Tolvaptan zu

bestimmen. MRT-Untersuchungen sind jedoch teuer, erfordern spezifische Expertise bei der Analyse und sind daher nicht immer verfügbar. Daher entwickelten wir einen in der Anwendung einfachen Test basierend auf demographischen Angaben der Patienten und Labordaten von 204 Patienten der Schweizer ADPKD Kohorte mittels Regressionsmodellen und einer anschließenden Bewertung des diagnostischen Tests. Ein sequentielles Triage Testverfahren erreichte eine Sensitivität von über 90%. Der Triage-Test kann zu einer besseren Allokation der Ressourcen führen, da Patienten, die (noch) nicht für eine Therapie mit Tolvaptan qualifizieren, mit einfach zugänglicher Information zuverlässig identifiziert werden müssen, für die keine MRT-Untersuchung nötig ist. In der dritten Studie führten wir schliesslich die erste Validierungsstudie eines prominenten Vorhersagemodells für den Verlauf der ADPKD durch, welche von Wissenschaftler der Mayo Klinik entwickelt wurde. Ein Vorhersagemodell ist im klinischen Umfeld nützlich zur Identifikation von Patienten mit einem erhöhten Risiko für einen schweren Verlauf, bei denen eine aggressivere Behandlung trotz Nebenwirkungen indiziert sein kann. In unserer zeitlich - und räumlich externen Validierung der zwei Mayo Klinik Modelle zeigte sich, dass die Modelle auf eine wesentlich andere Population (Schweizer ADPKD Kohorte) generalisierbar sind und diese eine valide Methode darstellen, um Patienten mit einem zu erwartendem schweren Verlauf zu identifizieren. Ein erweitertes Modell mit zusätzlichen Informationen zum Nierenvolumen verbesserte die Vorhersagekraft des Modells nicht wesentlich.

Die drei Studien dieser Dissertation tragen dazu bei, das zentrale Therapieziel der Verlangsamung der Krankheitsprogression zu verfolgen. Die hier entwickelten und untersuchten Triage-Tests und Vorhersagemodelle unterstützen evidenzbasierte Entscheide von Patienten und Ärzten zum Einsatz von aufwändigen diagnostischen Tests und zur Indikationsstellung von nichtmedikamentösen und medikamentösen ADPKD-Therapien.

Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic inherited renal cystic kidney disease and approximately 50 % of the patient's progress to end stage renal disease between the 5th and 6th decade of their life. A major therapy goal is to slow down disease progression. To achieve this, it is necessary to predict disease progression and to implement ADPKD management that balances the benefits, harms and cost appropriately. In 2016, tolvaptan was approved as the first drug to slow down disease progression in ADPKD and it is indicated for patients with rapid disease progression in Switzerland. Before the availability of tolvaptan, treatment focused on managing co-morbidities through medication and life style modification. This PhD thesis includes three studies, which contribute to an evidence-based management in ADPKD. The first study assessed the association between coffee consumption and disease progression in a longitudinal ADPKD cohort. The relentless progression of ADPKD means that most ADPKD experts are inclined to advocate the minimisation of risk factors for rapid disease progression such as caffeine consumption, despite the absence of clinical-epidemiological data indicating benefit. Our study results, which were, to our knowledge, based on the first longitudinal study that ensures temporality to assess the relationship between coffee consumption and disease progression, showed greater preservation of renal function and less kidney growth in patients who drank coffee compared to patients who did not. Thus, the evidence derived from our prospective longitudinal study, that allows more confidence for causal inference than previous in vitro or cross-sectional studies, does not support coffee drinking as a risk factor for ADPKD progression. The aim of the second study was to develop a triage test that identifies patients currently not meeting minimal TKV thresholds required for tolvaptan treatment and in whom TKV measurement can be avoided. This study addresses the challenge in ADPKD management that channels every patient to magnetic resonance imaging (MRI) or computer tomography (CT) to determine TKV, which is required to determine the

indication for tolvaptan. TKV is accurately measured by MRI, but the procedure is costly and not available everywhere. To our knowledge, there is no available low cost triage test for patients with ADPKD. We developed a simple triage tests based on commonly available demographic and laboratory data using regression models and performed a diagnostic test accuracy study using data from 204 patients enrolled in the Swiss ADPKD study. A sequential triage test reached a sensitivity of over 90%. A triage test for MRI-based TKV measurement supports clinical decision making for better resource allocation. The third study is the first external validation of the well-known Mayo Clinic models for predicting disease progression in ADPKD. Prediction models in ADPKD are useful in clinical settings for identifying patients with greater risk of rapid disease progression for whom a treatment may have more benefits than side-effects. The Mayo Clinic investigators developed a risk prediction tool for patients with ADPKD using a single TKV value. Our geographical and temporal external validation of the two Mayo Clinic models suggest that these models are generalizable to clinical settings with a high predictive performance and that the Mayo Clinic prediction model is an accurate tool with easily available predictors for identifying patients at high risk for rapid disease progression. Adding additional information on TKV did not improve the predictive performance to a meaningful extent. The three studies of this PhD thesis contribute to the major therapy goal of slowing down disease progression. The triage tests and prediction models developed and validated here support patient and physician evidence-based decisions on the use of diagnostic imaging and on the indication of non-drug and drug therapies. The results of this thesis open the door for the judicious use of expensive imaging tests and novel treatments. Additional studies in this area including randomized trials and cost-benefit analyses for estimating benefits, harms and cost of various testing and treatment pathways will ultimately inform clinical practice on the best management strategies that optimally balance benefits, harms and cost of patients with ADPKD**.**

Abbreviations

ADPKD	autosomal dominant polycystic kidney disease
cAMP	cyclic adenosine monophosphate
CRPS	continuous ranked probability score
CT	computer tomography
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
htTKV	height adjusted total kidney volume
MRI	magnetic resonance imaging
TKV	total kidney volume
PKD	polycystic kidney disease
RRT	renal replacement therapy

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Chapter I

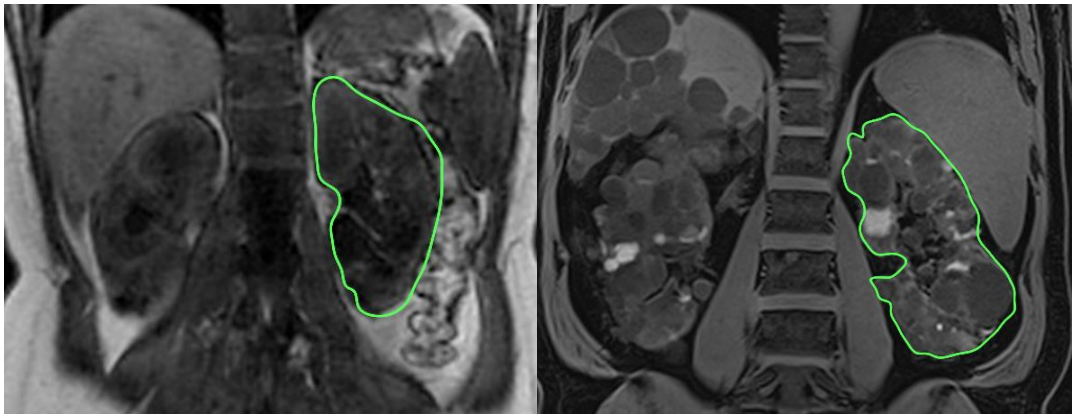
General Introduction

Introduction to Autosomal Dominant Polycystic Kidney Disease

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a monogenic inherited renal cystic kidney disease that occurs in all races worldwide [1]. ADPKD is the most common hereditary kidney disease, with an estimated prevalence of 1 in 1000 cases in the general population, but with a lower prevalence of symptomatic ADPKD [2, 3]. It is characterised by the development of a multitude of renal cysts, which leads to massive kidney enlargement (Figure 1) [4]. Approximately 50% of patients develop end-stage renal failure (ESRD) between the fifth and sixth decade of life and ADPKD is the fourth leading cause for renal replacement therapy (RRT) [4], which includes dialysis or kidney transplantation.

The pathogenesis of cyst formation begins *in utero* and the cysts enlarge continuously through the patient's lifetime via an autonomous function in each cyst. The renal cysts are interspersed within fibrotic tissue. Intracellular 3′ 5′-cyclic adenosine monophosphate (cAMP) plays a major causative role in the pathogenesis and disease progression of ADPKD by stimulating transepithelial secretion, the accumulation of cyst fluid and cell proliferation. Competitively and non-selectively inhibitory cyclic nucleotide phosphodiesterases degrade the phosphodiester bond in the second messenger molecule cAMP. More than 10 years' worth of research has revealed that increased levels of intracellular cAMP cause ADPKD progression by stimulating transepithelial secretion and cell proliferation [5, 6].

Figure 1: MRI of an ADPKD-affected kidney with cyst formation from the Swiss ADPKD Cohort Study (green line: kidney contouring)



The symptoms of ADPKD are correlated with renal enlargement. During a patient's life, blood may accumulate in the renal cysts following trauma or pyrogenic infection. The majority of patients experience other symptoms such as kidney pain and gross haematuria. The associated comorbidities of patients with ADPKD are hypertension, urinary tract infection and proteinuria. Hypertension occurs in 50% of patients in the early disease group, i.e. those aged 20–35 years, and in 100% of patients with ESRD [7]. Cyst enlargement also occurs in the liver, with a prevalence of 95% (by the age of 35 years) [8].

In almost all patients, the pathogenesis of ADPKD stems from a mutation of the genes encoding for the proteins polycystin-1 (*PKD1*) and polycystin-2 (*PKD2*). *PKD1* is located on chromosome 16 and its mutation is found in 85% of cases. *PKD2* is located on chromosome 4 and its mutation is found in around 15% of ADPKD cases [9, 10]. These mutations lead to the formation of distinctive fluid-filled renal cysts. Thus far, the mutations are not detected in around 1% of patients [11]. The clinical diagnosis of ADPKD in subjects with positive family history is confirmed when the number of cysts meet the Pei-Ravine diagnostic criteria for ADPKD [12, 13]. The Pei-Ravine criteria for ADPKD diagnosis specify age-dependant threshold for the number of cysts. 10-20% of the patients may not show a positive family history [14]. Genetic testing as a diagnostic test is useful when imaging cannot clearly

identify disease or for very early diagnosis in childhood. Two methods are used for ADPKD DNA-testing in equivocal cases: linkage analysis and direct mutation screening [15].

Current ADPKD Management

The main therapy goal in ADPKD is to slow down disease progression. In order to achieve this goal, clinicians need to predict the course of disease in an individual, use relevant outcomes to monitor disease progression, judiciously use imaging tests and pursue a decision making strategy that supports both non-drug and drug therapies options for patients.

Estimating prognosis in ADPKD

Prediction models in ADPKD are useful in clinical settings to inform patients about their prognosis and to support evidence-based decisions for risk-stratified treatment strategies where new therapies like tolvaptan are effective but have notable adverse effects. Patients with a slow disease progression might not need certain therapies or be best served by waiting until at a later disease stage for treatment. A few risk prediction models have been developed to support patients risk assessment: The Mayo Clinic Model [16] and the PROPKD-Score [17]. The major outcomes of relevance for ADPKD predictions models are End Stage Renal Disease (ESRD), total kidney volume (TKV) and estimated glomerular filtration rate (eGFR)[18], which form the basis for clinical determination of progression. In Europe, the average age for progression to ESRD is approximately 58 years [19]. Consistent and strong predictors of these outcomes include age, sex, TKV and eGFR at baseline as well as the Polycystic Kidney Disease (PKD)-genotype [20, 21].

Measuring relevant outcomes in ADPKD

The main outcomes in ADPKD are total kidney volume (TKV) and kidney function, estimated by the glomerular filtration rate (eGFR), which are indicators for disease severity

and progression. TKV is widely accepted as the main indicator for ADPKD progression. TKV is assessed by computer tomography (CT), the less sensitive renal ultrasonography or Magnetic Resonance Imaging (MRI), which is the gold standard, and it is used to measure the different size and volume parameters of the kidney. MRI, the preferred method for measuring TKV, can detect small cysts without requiring the use of ionizing or contrast media [16]. However, the measurement of kidney volume using MRI or CT is still not feasible for routine care in some countries (e.g. Australia, some countries in Europe) [22, 23]; therefore it is not available to a broad range of patients. The quality of the MRI depends on patient compliance and on various parameters, such as image sequences and slice thickness [24]. The state-of-the-art method for kidney volume computation is hand-contouring of the whole kidney, which is greatly time- and cost-intensive given the high technical expertise required, and this modality is still not routine in clinical practice. Two methods for estimating TKV: the eTKVellipsoid and the eTKVPANK, which require less time than hand contouring, have been developed [25]. While eTKVellipsoid measurement of the TKV is very accurate and convenient [26], the high expenses of performing MRIs and the reimbursement policies of the healthcare system may result in limited access to repeated MRIs for selecting patients for a new treatment as well as for detecting change in TKV [23, 27].

Sequential TKV measurement is a dynamic biomarker of disease progression with sufficient precision to detect changes over a period as short as 6 months [28]. TKV is used to monitor treatment effects, but TKV estimations are still limited. The strongest predictors of disease progression are: Annual rate of TKV growth, age, baseline glomerular filtration rate, gender and PKD genotype. Increased kidney size is associated with pain, gross haematuria and proteinuria [16].

Kidney function (eGFR) is very stable for a long period and serum creatinine levels only increase once there is serious and irreversible damage to the kidneys. The GFR is a late marker of disease. Therefore, renal function for disease progression is less indicative for

evaluating progression at early disease stage because it decreases exponentially with advanced age. Kidney enlargement eventually results in a decline in renal function. Historically, the true GFR is the average urinary inulin clearance measured over a period of 24 hours [29]. Three measurement methods have been developed to estimate GFR more easily, because in clinical practice it is not possible to measure eGFR over a 24-h period. Among them, the gold standard is Cr-EDTA or DTPA, often referred to as measured GFR (mGFR), where the clearance of iohexol or iothalamate is measured as filtration marker over a shorter period [30]. The second method is assessing the 24-hour clearance of creatinine or urea. This method is thought unreliable because creatinine clearance overestimates the true GFR and urea clearance underestimates the true GFR [31]. The third method is the use of an equation to estimated eGFR such as the MDRD (Modification of Diet in Renal Disease) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [32, 33, 34]. The CKD-EPI formula, which is the approach used most often in clinical practice, incorporates the variables serum creatinine, age, sex and race [34]:

$$eGFR = 141 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [if\ female] \times 1.159\ [if\ black]$$

Where Scr is serum creatine in mg/dL, K is 0.9 for males and 0.7 for females, and α is -0.411 for males and -0.329 for females.

Treatments options for ADPKD

Lifestyle factors are particularly important for the management of ADPKD patients for reducing risk factors and strengthening resources that can help prolong and stabilise renal function until ESRD. Therefore, behaviour modification has been credited with delaying disease progression in patients with ADPKD in the past. Avoiding high sodium/salt intake, avoiding smoking, low alcohol intake, reduced coffee intake, exercise, maintaining hydration

and healthy diet are relevant lifestyle factors for ADPKD [35]. Until recently, no disease-modifying therapy for treating ADPKD could prevent cyst formation and delay disease progression; only comorbidities could be treated [35]. General renoprotective treatment as such a low-protein diet, renin–angiotensin–aldosterone system inhibition and management of blood pressure control does not affect renal function decline in patients with ADPKD [36-39]. Over the years, several disease-modifying therapies have been tested in ADPKD. Based on the results of the TEMPO 3:4 trial, the 2016 approval of tolvaptan, a vasopressin V2 receptor antagonist that directly slows progression, heralded the first effective treatment for ADPKD [40]. The randomised, controlled TEMPO 3:4 trial involved 1445 patients with ADPKD with TKV > 750 mL and retained renal function over a follow-up duration of 3 years. The results showed that tolvaptan reduced the TKV growth rate by 49% and the eGFR decline rate by 26%. Vasopressin is a synthetic aquaretic, therefore it induced the main side effect of polyuria of up to 6–8 L per day. The indication for tolvaptan is currently limited to patients with evidence of rapid progression[41] where the expected benefit outweighs the risk of adverse effect and associated high treatment costs[42]. It is currently not clear yet how rapid disease progression should be determined.

Challenges and opportunities for the management of ADPKD

There are a number of challenges but also opportunities in ADPKD that will be addressed in this thesis:

1. Evaluate lifestyle factors such as coffee consumption that impact on disease progression in patients with ADPKD and that may be targeted to slow down disease progression

2. Evaluate which patients need elaborate imaging to determine rapid disease progression and develop tools for TKV-based management decisions for patients with ADPKD
3. Support the balancing of benefits and harms of interventions by the use of valid prediction models that predict disease progression

Effect of coffee for disease progression in an ADPKD cohort

Currently, there is a lack of evidence-based information about the effect for coffee for rapid disease progression. There is a requirement for greater understanding of the effect of coffee to optimise evidence-based management in ADPKD. The continuous progression of ADPKD and the lack of effective therapies until recently gave physicians and researcher little else to offer but strategies like minimization of caffeine consumption despite the absence of clinical and epidemiological data supporting their advice. *In vitro* results reported that caffeine activated pro-proliferative signalling pathways and increased transepithelial fluid secretion in murine PKD cells and the study concluded that caffeine is a risk factor for the promotion of cyst enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD) [27]. Since then, many ADPKD experts have advocated minimizing caffeine intake. However, there is little evidence on the effect of caffeine in patients with ADPKD and only cross-sectional studies have been presented in the literature. Since the current evidence base is very weak, there is a need for prospective and longitudinal studies to assess if there is a causal link between coffee consumption and disease progression.

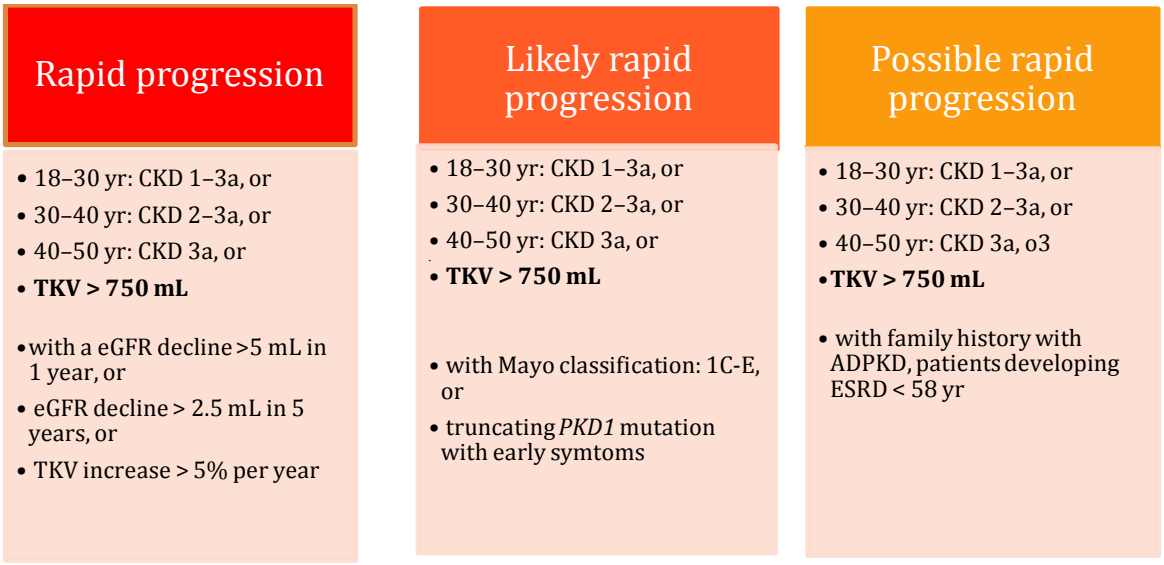
A tool for TKV-based management decisions for ADPKD patients would be attractice

Measuring TKV and TKV rate change as a surrogate for disease burden and progression has become even more important since the approval of tolvaptan in Switzerland. Based on the result of the TEMPO 3:4 trial, tolvaptan has been approved for those with a minimal TKV threshold and signs of rapid ADPKD progression [40]. Regulatory authorities have defined treatment eligibility as a TKV of at least 750 mL or a change in TKV of at least 5% [43]. However, accurate assessment of TKV, which is generally determined based on MRI imaging [26], is costly, requires expertise and is limited by health insurance reimbursement policies [23, 27]. This is an opportunity to develop a more low-cost, easily implementable tool for TKV-based management decisions to identify patients, who are unlikely to meet minimal TKV thresholds for treatment with tolvaptan and for whom unnecessary expenses could be spared.

Informing treatment decision through prediction models

Information about prognosis in ADPKD is essential for clinicians to inform patients about their further prognosis. Prediction models combine several patient characteristics and additional tests to predict the risk of a defined outcome. Prediction model in ADPKD supports evidence-based decision for risk-stratified treatment who might benefit more from new therapies such as tolvaptan, which is indicated for patients with evidence of rapidly progressing disease [41]. This treatment brings us the challenge to identify which patients we should treat and when should start the treatment of those patients. Patients with a slow disease progression might not need a therapy now or only at a later stage. In 2016, the ERA-EDTA Working Group outlined an algorithm for defining rapid disease definition in patients with ADPKD (Figure 4), which included the Mayo Clinic prediction model for classifying patients at high risk for rapid disease progression [23].

Figure 2: A convergence for an algorithm for defining rapid disease definition in patients with ADPKD, adapted and modified from [23]. CKD (chronic kidney disease); TKV threshold used in Switzerland for tolvaptan indication.



The Mayo Clinic investigators developed a risk prediction tool for ADPKD patients using a single TKV value and age at baseline [16, 44]. However, the prognostic performance of the prediction model has yet to be evaluated in an external population outside the US, which is critical for establishing accuracy and generalizability of risk discrimination across different patient populations [16]. Additionally, there is an opportunity to evaluate whether an improvement of the prediction performance could be achieved by including additional measurements.

Outline of the thesis

This PhD thesis contributes evidence on the management of ADPKD patients and addresses clinically relevant questions. Chapter II contains a paper focused on the effect of coffee consumption on ADPKD progression as assessed in a prospective and longitudinal cohort study of patients with early ADPKD. Chapter III focuses on a triage test for TKV-based management decisions for patients with ADPKD. The aim of that study is to develop a triage test that identifies patients currently not meeting minimal TKV thresholds required for tolvaptan treatment and in whom TKV measurement can be avoided. In chapter IV, we report the performance of an independent geographical and temporal external validation of the two Mayo Clinic models and the exploration of an updating strategy for improving the predictive performance by adding additional information on TKV. Finally, chapter V summarises the main results of the previous chapters and discusses their potential implications for clinical practice and research.

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Chapter II

Long-Term Effect of Coffee Consumption on Autosomal Dominant Polycystic Kidneys Disease Progression: Results from the Suisse ADPKD, a Prospective Longitudinal Cohort Study

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Abstract

Background: Previous in vitro experiments of human PKD cells reported that caffeine is a risk factor for the promotion of cyst enlargement in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). The relentless progression of ADPKD inclined the majority of physicians to advocate minimization of caffeine consumption despite the absence of clinical data supporting such a recommendation so far. This is the first clinical study which assessed prospectively the association between coffee consumption and disease progression in a longitudinal ADPKD cohort.

Methods: Information on coffee consumption and disease progression was collected at each follow-up visit using standardized measurement methods. The main model for the outcomes kidney size (htTKV) and kidney function (eGFR) was a linear mixed model. Patients entered to the on-going Swiss ADPKD study between 2006 to June 2014 and had at least one visit every year. The sample size of the study population was 151 with a median follow-up of 4 visits per patient and a median follow-up time of 4.38 years. Results: After multivariate adjustment for age, smoking, hypertension, sex, body mass index and an interaction term (coffee*visit), coffee drinkers did not have a statistically significantly different kidney size compared to non-coffee drinkers (difference of -33.03cm^3 height adjusted TKV, 95% CI from -72.41 to 6.34, p=0.10). After the same adjustment, there was no statistically significant difference in eGFR between coffee and non-coffee drinkers (2.03 ml/min/1.73m^2, 95% CI from -0.31 to 4.31, p=0.089).

Conclusion: Thus, data derived from our prospective longitudinal study does not confirm that drinking coffee is a risk factor for ADPKD progression.

Introduction

Belibi and colleagues reported 2002 results derived from *in vitro* experiments of human PKD cells exposed to caffeine [1]. Caffeine activated pro-proliferative signalling pathways and increased transepithelial fluid secretion in murine PKD cells and the authors concluded that caffeine is a risk factor for the promotion of cyst enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD) [2]. Caffeine raises intracellular adenosine 3':5'-cyclic monophosphate (cAMP) levels by competitively and non-selectively inhibiting cyclic nucleotide phosphodiesterases. These groups of enzymes degrade the phosphodiester bond in the second messenger molecules cAMP. For more than 10 years, intensive research has revealed that increased levels of intracellular cAMP causes ADPKD progression by stimulating trans-epithelial secretion and proliferation, thus further fostering the persuasion that caffeine consumption accelerates ADPKD progression [3, 4]. Since then, ADPKD experts and ADPKD patient organizations have advocated to minimize caffeine intake.

However, there is little evidence on the effect of caffeine in patients with ADPKD and only cross-sectional studies are available so far. In 2012 the results of a cross-sectional study in ADPKD and healthy volunteers investigating the difference in caffeine intake and renal volume were reported [5]. Vendramini and colleagues did not identify an association of caffeine intake and kidney size, whereas the intake of caffeine was much lower among ADPKD patients than in healthy volunteers. Possibly the observed caffeine consumption difference among ADPKD patients and healthy volunteers was due to the conviction in the ADPKD community that caffeine might be toxic for ADPKD patients, although these concerns were based solely on *in vitro* human cell experiments [6].

The relentless progression of ADPKD and the lack of effective therapies until recently inclined the majority of physicians to advocate minimization of caffeine consumption despite the absence of clinical data supporting their advice. In fact, cohort studies in human beings repeatedly showed a beneficial effect of coffee consumption on various outcomes. Coffee consumption has been associated with decreased mortality in a meta-analysis of nearly one million subjects in 21 different independent studies [3, 7]. Coffee drinking's beneficial effects have been identified for various diseases including cardiovascular and kidney diseases [8-10].

Since the current evidence base is very weak, our aim was to assess the longitudinal association of coffee consumption and the progression of disease in patients affected by ADPKD.

Methods

Study Design and Participants

Patients were eligible for our analysis if they were enrolled from 2006 to 2014 in the Swiss ADPKD cohort and if they had not been treated with possible disease modifying drugs (e.g. Sirolimus, Everolimus, Tolvaptan, Somatostatin analogues). Patients had a proven ADPKD diagnosis, were between 18 and 60 years old and had an eGFR over 30 ml per min per 1.73m^2 at enrolment to the cohort. All patients provided a written informed consent and the local ethic committee approved the study (EK-number 1178). Possible serious adverse events and adverse events have been reported to the investigator of the study at least at every study visit. The included patients had a minimum of 1 and a maximum of 8 follow-up visits (median: 4 visits) and a median follow-up time of 4.38 years (IQR: 2.16 to 6.1 years). At each study visit the medical history was obtained, including medication, complications related to ADPKD, and the daily consumption of caffeine [11]. We excluded 69 patients with

less than 2 visits because our study focused on disease progression over time, leading to a total sample size of 151 patients with 687 observations.

Progression of disease

Our primary outcome for progression of disease was kidney size by using height adjusted total kidney volume (htTKV) and the secondary outcome was the glomerular filtration rate (GFR). The baseline visit and each follow-up visit included a measurement of the kidney size and function by using a standardized procedure protocol. The Magnetic Resonance Imaging acquisition consists of breath-hold T1-weighted fast spoiled gradient echo sequence without fat suppression sequence (4 mm slice thicknesses) and a trans-axial T2 weighted fast spin echo sequences. The total kidney volume was estimated by hand contouring of all MRI slices. The observer was blinded for previous measurements. Manual volume segmentation was done with the computer workstation advantage windows workstation 4.4, GE Healthcare[12]. At each study visit, serum creatinine with the use of the modified Jaffé method traceable to an isotope-dilution mass spectroscopy reference was assessed[13]. GFR was estimated by applying the CKD-EPI formula[14].

Coffee consumption

Coffee consumption was assessed at each visit according to the following categories: Never drinking coffee; less than one cup of coffee per day, one or two cups of coffee per day, two to four cups of coffee per day, and more than four cups of coffee per day. For the analysis, coffee consumption was summarised in a binary variable, as “No drinking or less then one coffee a day” and “coffee drinkers”. If the information about coffee consumption was missing for a certain visit (number of missing values: 162), the last available information

was used for the analysis. We also performed a sensitivity analysis without imputation of missing values.

Potential confounders

We considered the following potential confounders in the analyses that may bias the association of coffee consumption and progression of ADPKD: At each visit, anthropometric measurement and laboratory examinations were performed including height-, weight- and -blood pressure measurement as well as various blood and urine analysis. BMI (kg/m^2) was included as a continuous variable. Blood pressure was measured in a sitting position, two times at an interval of 10-minutes, by using an oscillometric blood pressure device (Boso-Medicus, Jungingen, Germany). The variable hypertension was defined as either systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg and/or taking antihypertensive medication. Smoking was summarised in a binary variable, as "yes" and "no".

Statistical Analysis

Baseline characteristics are given as proportions, means (± standard deviation) and median (interquartile range, IQR), depending on their distribution. The main model for the primary outcome kidney size (htTKV) was a linear mixed model, with htTKV as outcome and coffee consumption as exposure, and adjustment for confounders (baseline age, sex, hypertension, smoking and BMI). We included a random intercept for each subject and a random slope for each subject over time in the mixed model. Most of the covariates were time-varying (coffee, hypertension, smoking and BMI) except of two which were fixed (baseline age and sex) [15]. Mixed models allowed us to track subject-specific change over

time and take into account the fact that data from the same individual are not independent. P-values of <0.05 were considered significant. Stata 13.1 was used for data analysis.

Results

Patient characteristics

At inclusion (from April 2006 to June 2014) all 220 patients had a proven ADPKD diagnosis. The remaining 151 ADPKD patients with 687 observations were included in the analyses. At baseline, 101 (67%) patients were coffee drinkers whereas 50 (33%) patients did not drink coffee. Their overall mean ± SD age was 32.8 ± 8.9 years, and 60 (40%) were female. Non-coffee drinkers compared to coffee drinkers (Table 1) were younger (28 ± 8 years vs. 35 ± 8 years), their kidneys at baseline were smaller (753 cm^3 vs. 1118 cm^3), and their renal function was better (eGFR 95.8 ± 19.5 ml/min/1.73m^2 vs. 88.2 ± 19.1 ml/min/1.73m^2). The majority of patients suffered from hypertension (26 (52%) of the non-coffee drinkers and 69 (68%) of the coffee drinkers).

Table 1. Demographic, clinical, and laboratory data at enrolment (baseline) according to coffee consumption group

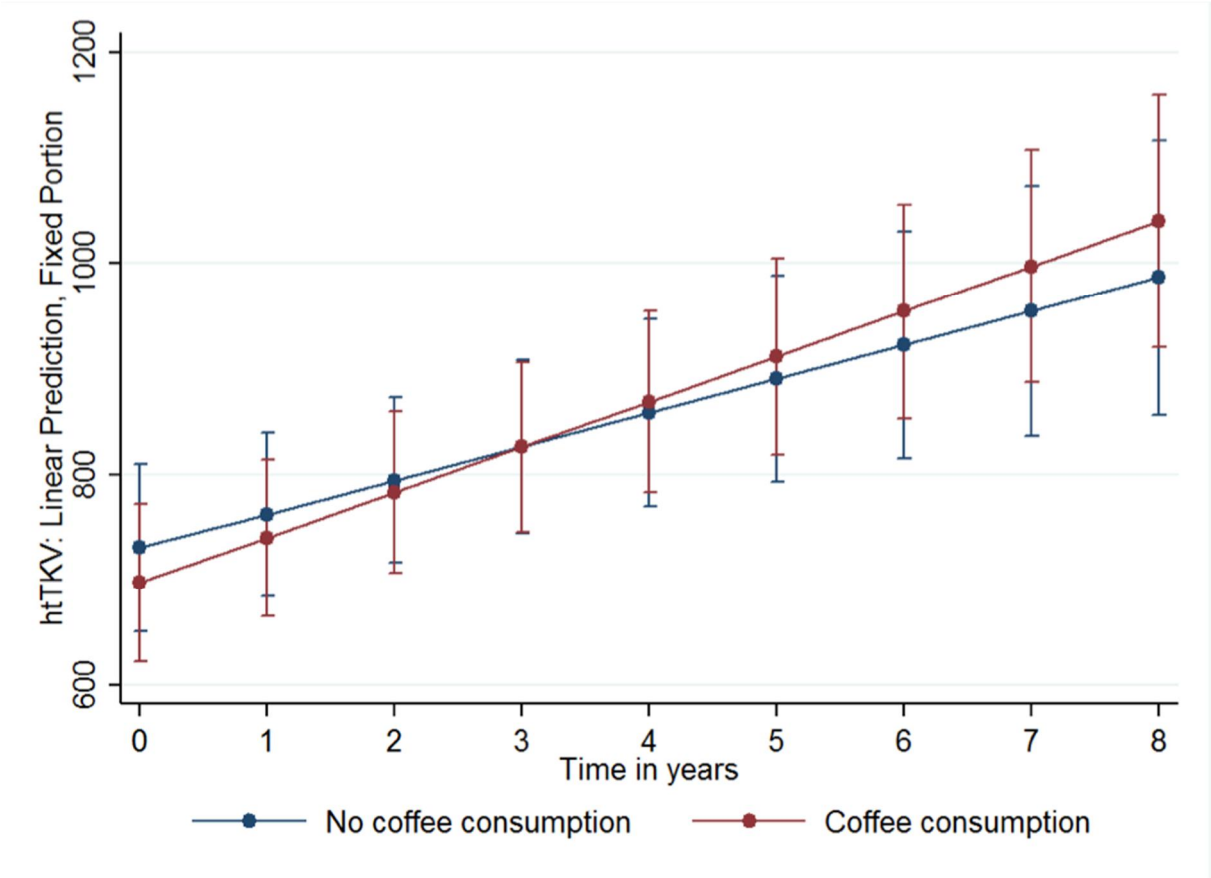
Characteristic	**Total**	**No Coffee drinkers**	**Coffee drinkers**
	N=151	**N=50**	**N=101**
Age – years	32.8 ± 9	27.92 ± 8	35.2 ± 8
Sex ï no. (%)			
Female	60 (40)	23 (46)	37(37)
Male	91 (60)	27 (54)	64 (63)
BMI – kg/m^2 (Mean± SD) (Missings=9)	24.04 ± 4	23.62 ± 4	25.38 ± 4
eGFR – ml/min/1.73m^2 (Missings=2)			
Mean± SD	90.78 ± 19	95.8 ± 19	88.23 ± 19
Median (IQR)	89.24 (78 to 104)	97.01 (82 to 113)	87.04 (75 to 102)
Smoking ï no. (%)	53 (36)	16(33)	37 (37)
TKV – cm^3			
Mean± SD	1050.8± 685	915.8± 632	1117.8 ± 703
Median (IQR)	894.51 (576 to 1306)	752.56 (492 to 1038)	976.43(603 to 1372)
htTKV – cm^3/m			
Mean± SD)	595.9 ± 382	519.3±364	633.9± 87
Median (IQR)	504.56 (333 to 732)	421.7 (268 to 613)	549.03 (353 to 762)
Hypertension – no. (%)	95 (63)	26 (52)	69(68)
Blood pressure ï mmHg (Missings=2)			
Systolic (Mean± SD)	138.4 ± 14	136.5± 13	139.4 ± 15
Diastolic (Mean± SD)	89 ± 10	86.2± 9	90.5 ± 11
Antihypertensive Drug – no. (%)	107 (71)	32 (64)	75 (74)

Association of coffee consumption with kidney progression

We found in the adjusted mixed model for height adjusted TKV (htTKV) a smaller estimated kidney size among coffee drinkers compared to non-coffee drinkers ([beta]$_{Coffee}$ = -33.13; 95% CI from -72.52 to 6.34; p=0.10) but the difference was not statistically significantly different. The interaction term between coffee and time in years was also not statistically significant ([beta]$_{Coffee*Visityr}$ = 10.85; 95% CI from -1.89 to 23.58; p=0.10), indicating only week evidence for a steeper increase of htTKV in coffee drinkers over time.

The time variable was significant in all analyses ([beta]$_{Visityr}$ = 49.32; 95% CI from 35.49 to 63.10; p=<0.01). Fig 1 illustrates the development of htTKV over time from the mixed model taking into account an interaction between time (in years) and coffee. The lower baseline values of coffee drinkers as well as the steeper slope over time are clearly visible.

Fig 1. Adjusted prediction of kidney size (height adjusted total kidney volume (htTKV)) with 95% CI, by coffee consumption group



A sensitivity analysis included the alternative time variable "number of visits since enrolment" instead of time in years and "age" as time-varying covariate (instead of age at baseline) and showed similar results (Table 2) as the main model. A repetition of the analysis for subjects with more than 2 visits (omitted if < 3 visits per subject) confirmed our results. An additional sensitivity analysis without imputation of missing values for coffee showed similar results and confirmed the main analysis (Supplementary data table 1).

Table 2. Association of coffee consumption with adjusted kidney size (height adjusted total kidney volume (htTKV)) over time (N=148)

Main Analysis: htTKV with visit in years and baseline age			
Fixed effects			
Name	Coefficient	p-Value	95% -CI
(Intercept)	222.19	0.14	from -76.86 to 521.25
Coffee	-33.13	0.10	from -72.52 to 6.34
Visityr	49.32	<0.01	from 35.49 to 63.10
CoffeeVisityr	10.85	0.10	from -1.89 to 23.58
Sex	-204.56	<0.01	from -316.18 to -91.19
Age Baseline	17.30	<0.01	from 11.25 to 23.67
BMI	4.78	0.08	from -0.57 to 10.14
Hypertension	-13.01	0.27	from -36.55 to 10.42
Smoke	-6.27	0.59	from -29.27 to 16.72
Random Effect			
Group		Name	Variance
Patno	(Intercept)	333.75	19.72
Visityr		59.05	3.93
Residual		47.43	1.77
Sensitivity Analysis: htTKV with visit number and age (time-dependent)			
Fixed effects			
Name	Coefficient	p-Value	95% -CI
(Intercept)	-2.67	0.99	from -296.45 to 291.10
Coffee	-66.63	0.02	from -123.85 to -9.42
Visite (Nr)	12.67	0.01	from 2.73 to 22.61
CoffeeVisit	10.17	0.03	from 1.07 to 19.26
Sex	-189.02	<0.01	from -297.85 to -80.20
Age	24.60	<0.01	from 18.93 to 30.27
BMI	3.41	0.28	from -2.78 to 9.60
Hypertension	-13.95	0.33	from -42.06 to 14.17
Smoke	-7.32	0.61	from -35.17 to 20.54
Random Effect			
Group		Name	Variance
Patno	Intercept	318.12	19.90
Vist (Nr)		36.00	2.42
Residual		57.43	2.16

Association of coffee consumption with eGFR

The main mixed model for eGFR was adjusted for the same confounders as the model for htTKV (Table 3). We can see that eGFR was estimated to be higher among coffee compared to non-coffee drinkers (2 ml per min per 1.73 m2 ($[beta]_{Coffee}$ = 2.03; 95% -0.31 to 4.38, p=0.089), however, this effect was again not statistically significant. Fig 2 illustrates our mixed model's adjusted predictions of eGFR with 95% CI.

Fig 2. Adjusted prediction of kidney function (estimated glomerular filtration rate (eGFR)) with 95% CI, by coffee consumption group

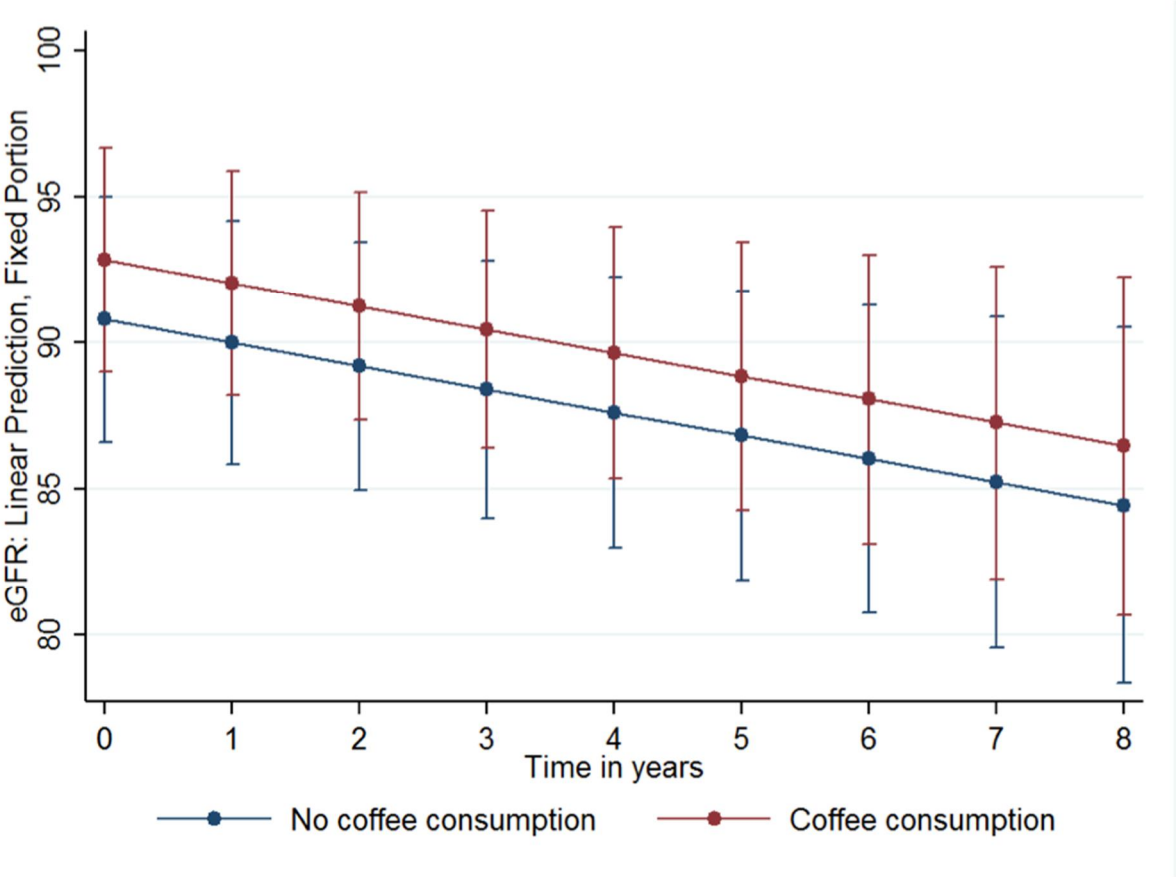


Table 3. Adjusted association of coffee consumption with kidney function (estimated glomerular filtration rate ml/min/1.73 m^2 (eGFR)) over time (N=148)

Main Analysis: eGFR with visit in years and baseline age			
Fixed effects			
Name	Coefficient	p-Value	95% -CI
(Intercept)	140.67	<0.01	from 124.38 to 156.96
Coffee	2.03	0.089	from -0.31 to 4.38
Visityr	-2.13	<0.01	from -2.67 to -1.59
Sex	0.48	0.854	from -4.69 to 5.67
Age Baseline	-1.34	<0.01	from -1.62 to -1.05
BMI	-0.17	0.418	from -0.58 to 0.24
Hypertension	-3.56	<0.01	from -5.98 to -1.15
Smoke	-1.81	0.141	from -4.22 to 0.59
Random Effect			
Group		Name	Variance
Patno	(Intercept)	14.35	0.92
Visityr		2.44	0.23
Residual		6.21	0.22
Sensitivity Analysis: eGFR with visit number and age (time-dependent)			
Fixed effects			
Name	Coefficient	p-Value	95% -CI
(Intercept)	142.86	<0.01	from 126.92 to 158.79
Coffee	2.13	0.079	from -0.24 to 4.52
Visit (nr)	-0.46	<0.01	from -0.83 to -0.08
Sex	0.08	0.975	from -5.04 to 5.21
Age	-1.37	<0.01	from -1.64 to -1.09
BMI	-0.18	0.385	from -0.59 to 0.23
Hypertension	-3.35	<0.01	from -5.78 to -0.92
Smoke	-1.51	0.223	from -3.93 to -0.92
Random Effect			
Group		Name	Variance
Patno	(Intercept)	13.97	0.93
Visit (Nr)		1.56	0.14
Residual		6.22	0.22

The sensitivity analysis with the time variable number of visits since enrolment and adjusted for age as a time-varying covariate (instead of age at baseline) showed similar results as the main analysis. As in the former section, the analysis for subjects with more than 2 visits (omitted if < 3 visits per subject) showed very similar results. An additional

sensitivity analysis without replacing missing values for coffee confirmed the results of the main analysis (Supplementary data table 2).

Discussion

In our prospective longitudinal study of an ADPKD cohort at early disease stage, we did not find a statistically significant association between coffee consumption and disease progression as measured by kidney volume and function. The main analyses were corroborated by the sensitivity analyses, which assessed if results changed by including predictors for ADPKD progression as time-varying covariates. The examination of the relationships between htTKV and age as a time-varying covariate showed similar results for the slope whereas the interception point of the trajectory lines was higher, (approximately for 4 visits). Our findings indicate that drinking coffee is unlikely to be a risk factor for disease progression in ADPKD patients.

One may speculate if coffee consumption even has some protective effect. The point estimates for kidney volume and function favour the coffee consumption group although not statistically significantly so. The effect might change over time as Figs 1 and 2 show. The protective effect on kidney volume may diminish over time, whereas the effect of coffee consumption on kidney function was constant over time.

In fact, cohort studies in human beings have well investigated the effect of coffee consumption on various outcomes and repeatedly showed a beneficial effect. A community-based study from Hsu et al. has investigated risk factors for chronic kidney disease including coffee consumption. After adjustment, coffee consumption was associated with a lower risk of chronic kidney disease [16]. Three large cohort studies published in 2014 have investigated the association between coffee consumption and the incidence of kidney stones. Drinking coffee was independently associated with a lower risk of incident kidney

stones [17]. Coffee consists of more than caffeine, it is also rich in antioxidants, which has been attributed for many of its health benefits [18]. Previous studies reported that coffee can have a positive effect on health and is a protective factor on avoiding diabetes, cancer (skin, breast, neck and head), stress, Parkinson's disease and also heart disease [8-10]. Besides these observations, other studies have also reported negative effects of coffee consumption on blood pressure, cholesterol, serum lipids levels, and insulin resistance [19-22]. A dose response meta-analysis of 21 longitudinal studies with nearly 10 000 00 subjects showed a non-linear association between coffee and mortality from all causes, cardiovascular disease and cancer. The highest risk reductions were observed by drinking 4 cups per day for all-cause mortality and 3 cups per day for cardiovascular mortality. Drinking coffee was not associated with increased mortality due to cancer [7]. Therefore, transferring the strong evidence of a protective effect of a moderate coffee consumption from other diseases may imply, that drinking coffee may also be beneficial for ADPKD patients in general through antioxidant and anti-inflammatory effects. And indeed, our results contravene the general recommendation to avoid drinking coffee for patients affected by ADPKD.

Currently, Tolvaptan as a disease modifying therapy is available in Japan, Canada, States and Europe, the latter of which has recently been approved [23]. Before, only co-morbidities could be treated. Beside this new medical treatment, lifestyle factors are particularly important for ADPKD patients to reduce risk factors and strengthen resources that can help prolonging and stabilizing renal function until end stage renal disease (ESRD). Therefore, avoiding potential risk factors in lifestyle, have been attributed a relevant role to delay the disease progression in patients with ADPKD in the past.

Our results have to be interpreted in the context of the study design and setting. Firstly, one limitation is the measurement of coffee consumption as the only source of caffeine (e.g. no soda, black tea or energy drinks were evaluated). Although it is difficult to capture coffee consumptions differently, self-reported coffee consumption may be prone to misclassification, which may result in biased results. A limitation of our study is that self-reported coffee consumption does not include other source of caffeine like cola, energy drinks and black tea. Secondly, the number of follow-up visits may still be too low and we may have missed important long-term effects. Moreover, our subjects did not routinely undergo genetic testing during the study visits. However, based on the mean annual kidney growth rate of 9.43 % and the median kidney size at baseline of 894.51 cm^3, it is very likely that the vast majority of our patients have PKD1 mutations.

Strengths of the presented study include its longitudinal design, the comprehensive statistical approach, the careful measurement of kidney volume and function and the well-described cohort of untreated ADPKD patients at early disease stage.

We believe that our results are a major step forward to elucidate the role of coffee consumption in ADPKD patients. The current evidence in patients with ADPKD including this longitudinal study does not suggest an association between coffee consumption and disease progression. It may be too early to frame a recommendation for coffee consumption but it is time to at least lift the current recommendation to strictly avoid coffee consumption. In order to come up with stronger and evidence-based recommendations additional studies are needed to strengthen the causal inference on coffee consumption and disease progression. Additional prospective cohort studies would show how consistent the results are across studies, if there is a dose-response relationship, if there are subgroups of ADPKD patients

who have different effects of coffee consumption and if longer follow-up reveals a protective effect of coffee consumption.

In conclusion, this is the first prospective longitudinal study to investigate the long-term effect of coffee consumption in an ADPKD population, carefully controlled for confounding. Our results suggest that drinking coffee is not a risk factor of ADPKD progression and question the current recommendations against coffee consumption.

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Chapter III

Is a triage test for management TKV decision useful to select patients for a treatment pathway in autosomal dominant polycystic kidney disease?

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Submitted

Abstract

Total kidney volume (TKV) is an important outcome for assessing disease severity in patients with autosomal dominant polycystic kidney disease (ADPKD). TKV has become the primary metric for assessing progression, as regulatory authorities have defined minimal TKV thresholds and TKV rate changes for determining eligibility for tolvaptan treatment. TKV can be accurately measured by magnetic resonance imaging (MRI); however, MRIs are costly and not universally available. The aim of our study was to develop a triage test to identify patients unlikely to meet minimal TKV thresholds required for tolvaptan treatment for whom TKV measurement via MRI can be avoided. We developed a simple triage test based on TKV estimation from generally available demographic and laboratory data. Predictors for the estimation formula were selected using least absolute shrinkage and selection operator (lasso). We assessed the diagnostic accuracy of final triage algorithms using data from 204 patients enrolled in the on-going Swiss ADPKD study to detect patients with TKV above 750 mL. Two decision thresholds applied to estimated TKV values from two different models were evaluated for discrimination accuracy. A decision threshold of 750 mL with a parsimonious estimating equation resulted in a sensitivity of 82% while a decision threshold of 675 mL resulted in a sensitivity of 87%. Our results suggest that a diagnostic management strategy using standard clinical data as the basis for a triage test can support decision making and aid allocation of medical resources, potentially reducing medical costs and unnecessary imaging procedures.

Keywords: ADPKD, chronic kidney disease, kidney development, vasopressin

Introduction

Total kidney volume (TKV), a measurement of kidney size, is an accepted surrogate for disease severity and a common outcome measure in clinical trials evaluating treatment efficacy in patients affected by autosomal dominant polycystic kidney disease (ADPKD). Positive change in TKV over sequential measurements reflects cyst enlargement and thus TKV serves as a sensitive marker of disease progression [1-3]. Changes in kidney size of as little as 20 cm^3 can be detected from repeated MRI measurements [4]. Thus while other predictors of disease progression exist including age, estimated glomerular filtration rate (eGFR) and Polycystic Kidney Disease (PKD)-genotype, TVK and its growth rate are considered the gold standard for defining ADPKD progression [1,5,6].

Measuring TKV and TKV rate change as a surrogate for disease burden and progression has become even more important since the approval of tolvaptan, a vasopressin V2 receptor antagonist that slows disease progression. Based on the result of the TEMPO 3:4 trial, tolvaptan has been approved in Canada, Japan, European Union and Switzerland for those with a minimal TKV threshold and signs of ADPKD progression [7]. Regulatory authorities have defined treatment eligibility as either: 1) a TKV of at least 750 mL or 2) a change in TKV of at least 5% [8]. Among ADPKD patients, the prevalence of TKV ≥750 mL was 58% in the CRISP Study [3] and 56% in the Swiss ADPKD Study, suggesting that approximately half of the current patient population may meet these eligibility criteria. However, accurate assessment of TKV, which is generally determined based on MRI imaging [9], is costly, requires interpretation expertise and is limited by health insurance reimbursement policies [10, 11]. Thus, the development of a low-cost, easily implementable triage test to identify patients who are unlikely to meet minimal TKV threshold for treatment with tolvaptan could prevent unnecessary expense and medical personnel time.

An optimal triage test would be based on easily obtainable parameters captured during regular care, have high sensitivity and at least moderate specificity. A high sensitivity would ensure that those most likely to qualify for tolvaptan treatment are selected for further testing (low false negative rate); a moderate specificity would reduce the number of unnecessary tests by removing most of the patients who are unlikely to qualify for treatment (modest false positive rate) [12, 13].

To our knowledge, there is no triage test for ADPKD patients, although the potential of such a decision tool for saving resources could be substantial, assuming a 50% prevalence of treatment eligibility in ADPKD patients aged 18 to 45 years. Therefore, the aim of our study was to develop a triage test based on TKV prediction from easy accessible clinical parameters to screen ADPKD patients for further MRI imaging and evaluate its performance given two proposed decision thresholds of 750 mL and 675 mL.

Results:

Baseline characteristics

204 patients with ADPKD between April 2006 and October 2016 were included in the analysis. Forty-three patients with missing baseline information on TKV, eGFR and age were excluded. The median age at baseline was 33 years (interquartile range [IQR]: 26-39), the median eGFR at baseline was 82 mL/min per 1.73 m2 (IQR: 72-96) and the median TKV at baseline was 858 mL/m (IQR: 565- 1354)

TKV estimation formula

A total of 146 subjects with complete data for all 49 variables of interest were used in least absolute shrinkage and selection operator (lasso) regression to select important predictors of TKV. Table 2 shows the result for both a parsimonious estimating equation (basic equation) and an extended estimating equation (extended equation) for TKV.

Estimation equation performance

The basic equation had an R^2 of 47%. Fifty-two percent of the predicted TKV were within 30% of the true TKV and the RSME was 0.45. When additional blood parameters were included, the resulting extended equation had a modestly higher R^2 of 52%, 55% of the predicted TKV values were within 30% of the observed TKVs and the RSME was 0.43. Table 3 shows the performance of the basic and extended equations (Supplement figure 1). The extended model had slightly improved concordance between the estimated and measured TKVs at 68% compared to 64% for the basic model. The bias (median difference) was also modestly reduced with the extended model.

Performance of the triage test

Using the basic equation, a decision threshold of 750 mL resulted in a sensitivity of 82% and a specificity of 64% (table 4). Applying a lower decision threshold of 675 mL resulted in a sensitivity of 87% and a specificity of 53%. The area under the curve (AUC) for the basic equation was of 0.83 (Figure 1).

When TKV was estimated with the extended equation, a decision threshold of 750 mL resulted in a sensitivity of 85% and a specificity of 64%. Applying a lower decision threshold of 675 mL resulted in a sensitivity of 92% and a specificity of 55% (Table 2,). The AUC for the extended equation was of 0.85 (Fgure 1).

Performance of a sequential test after 1-2 years of follow-up

Given changes in the characteristics of the sample at a second testing time point, the TKV estimation model was refit and new parameter estimates were obtained for the covariates flank pain, macrohematuria and coffee consumption (supplementary data table 1). A basic formula for a second test using a decision threshold of 750 mL resulted in a sensitivity of 53% and a specificity of 96%. Applying a lower decision threshold of 675 mL resulted in a sensitivity of 64% and a specificity of 91% (table 4).

Adding a second test and a maximum of 2 years of follow-up substantially improved overall sensitivity with the extended model and a threshold of 750 mL yielding an overall sensitivity of 92%. Using the more conservative threshold of 675 mL resulted in an overall sensitivity of 95%. Results were very similar for the basic model, with an overall sensitivity of 91% with a threshold of 750 mL and a sensitivity of 95% for a threshold of 675ml.

Expected decision-making for a hypothetical population of 1000 patients

Figure 2 shows the expected natural frequencies along each clinical pathway based on the four models. The basic equation with a threshold of 675 mL resulted in the detection of 38 more true positives per 1000 patients compared to the threshold of 750 mL. The extended equation detected a higher numbers of true positive patients at both thresholds compare to the basic equation, but the conservative threshold of 675 mL resulted in 36 more true positives per 1000 patients compared to the threshold of 750 mL.

Applying a second test 2 years later resulted in the detection of 59 additional true positives per 1000 patients with a threshold of 750 mL. Applying the more conservative threshold of 675 mL resulted in 46 additional true positive patients.

Discussion

Here we evaluated the performance of a triage test for identifying ADPKD patients unlikely to meet minimal eligible criteria for tolvaptan treatment, as currently defined by care guidelines. We found that applying either a 750 mL or a 675 mL decision threshold to an estimated TKV yielded sensitivity of greater than 90% after sequential testing. A comparison of a basic and an extended TKV estimating equation indicated that age, height, eGFR, weight, sex, hypertension, coffee, blood pressure and presence of symptoms were sufficient indicators of TKV, and the addition of diastolic blood pressure (bpd), sodium, cholesterol, high density lipoprotein (hdl) and urea did not result in markedly improved predictive performance that would warrant the added requirement of availability of these laboratory measurements.

Given the high sensitivity that can be achieved with a basic triage test using ubiquitously measured ADPKD disease indicators, such a procedure would be feasible to implement in routine ADPKD clinical care. There are cost and staff burden benefits of reducing the number of MRIs done on patients in care, even in clinical care centers with dedicated MRI acquisition protocols and trained personnel to measure TKV. To date, MRIs for assessment of TKV are not reimbursed in some countries (e.g. Australia) [10, 14]. A clinical decision-making tool for triaging patients towards or away from additional MRI screening could form the basis of a reimbursement policy. Furthermore, patients in countries with less developed health care systems could benefit from a more efficient allocation of MRI resources.

An alternative measurement modality for TKV-based management decisions is ultrasound (US), which is mostly used for pre-symptomatic screening of individuals at risk

for ADPKD [15]. Measuring TKV via US does not reduce costs and the inter-operator variability has been found to be too high to allow short-term progression to be detected [16-18]. For clinical trials [4] and drug prescription [19], precise measurement of TKV is required and can only be obtained by MRI or CT [20, 21]. Thus, US would not be a practical substitute [19].

In applying decision thresholds, we assumed that modest numbers of false negatives were acceptable, as sequential testing would later detect these patients before much additional progression had occurred. However, there are costs in terms of patient quality of life and increased damage to the kidney associated with delay of treatment, which are difficult to quantify. A lower decision threshold may be more appropriate in contexts where additional MRIs are less burdensome.

Additional studies are warranted to estimate the costs and benefits associated with a triage test. Though a formal cost effectiveness analysis was beyond the scope of the current paper, at an approximate estimated billing costs of 850 $ per MRI suggest that the expected cost per 1000 patients of universal MRI imaging is $850'000, while the expected MRI costs under presented scenarios including a triage test ranged between $585'650 to $640'900 (Figure 3). However, additional factors need to be considered, such as the impact of a delayed detection of disease stage and a later initiation of tolvaptan. There are also ethical considerations. Tolvaptan delays the progression to end stage renal disease by up to 120 days per year. Whether rationing treatment is reasonable and the ADPKD care community can justify limiting access to the benefit of therapy may continue to be debated. Certainly there are harms associated with tolvaptan use that warrant careful monitoring in treated patients.

In conclusion, a diagnostic management strategy using a triage test based on estimation of TKV can provide sufficient accuracy for better resource allocation; in contexts where additional MRIs are less burdensome a lower decision threshold may be more appropriate.

Methods

Study Participants

The on-going prospective observational Swiss ADPKD study has been described previously [22-24]. For the current study, we included participants that were under active follow-up between 2006 and 2016, who had not yet been treated with tolvaptan. Patient visits occurred at the University Hospital in Zurich (USZ) and at the Hirslanden Clinic in Zurich. The local ethics committee in Zurich approved the study (EK-number 1178).

Available clinical variables

Data were available from clinical visits, which occurred at intervals according to clinical need. TKV was measured by using a standardized procedure protocol [25] TKV was estimated by hand contouring or by midslice method to estimate TKV after 2015 [26, 27]. At the baseline and follow-up visit, GFR was estimated using the CKD-EPI formula [28]. Blood pressure, height and weight were assessed at each visit, and both blood and urine samples were taken using standardized laboratory procedures.

Hypertension was defined as either systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg and/or antihypertensive medication use. Smoking was summarised in a binary variable, as current or former/never. Coffee consumption

(yes/no) was based on self-report. The presence of flank pain, macrohematuria or/and cyst infection were captured from a case report form completed during the clinical visit.

Development of the triage test

Using data from all participants with compete data on all clinical variables, Lasso regression was used to screen all available clinical measures to identify the strongest predictors of TKV. The Lasso operator adds a penalization term to the magnitude of the regression coefficient and minimizes the sum of errors towards zero [29]. Parameter estimates from linear regression for the outcome of natural log of TKV were evaluated for inclusion in the final TKV estimation formula. Out of the Lasso regression, we included the variables bpd sodium, cholesterol, hdl and urea on the natural scale into the model; blood haemoglobin was left out because of too little additional added value. In addition, we developed a basic model for estimating log TKV, which included only the baseline predictors age, height, eGFR, weight, sex, hypertension, coffee and symptoms.

For the sequential second test in the testing pathway, we refit the TKV estimating equation and included for the outcome log TKV the parameter estimator's eGFR, weight, sex, hypertension, blood pressure diastolic, blood pressure systolic, coffee, age, single symptoms of flank pain and macrohematuria.

Metrics for estimating equation performance:

We used Bland Altman analysis to compare measured and estimated TKV for each patient at baseline and assessed any bias as the median difference, where a positive value indicated an overestimation of TKV. The precision of the model was tested by calculating the interquartile range (IQR) for the difference. To assess the accuracy of the model the root

mean square error (RMSE) and the P30 (percentage of estimated TKV within 30% of measured TKV) were calculated.

Metrics for triage test accuracy

The diagnostic accuracy of the estimation equation was determined by assessing agreement between those selected by the triage test and those eligible for tolvaptan treatment based on MRI measurement of TKV. Sensitivity and specificity were calculated for each estimation equation and decision threshold; the area under the curve (AUC) was also estimated for each TKV estimation equation [30]. For sequential triage tests an overall test accuracy was calculated.

Two decision thresholds were evaluated: TKV 750 mL and TKV 675 mL. The threshold of 750 mL aligns with current eligibly criteria for tolvaptan treatment based on results from the Tempo 3:4 trial [31]. A more conservative threshold of 675 mL was also evaluated, which corresponds to a variability of 10% or to the growth of TKV over 2 years assuming a kidney-growth rate of 5%.

In order to translate the accuracy of the triage to a meaningful metric, we used natural frequencies (starting with 1000 ADPKD patients) to illustrate how many patients would undergo further testing with MRI or not be tested based on the results of the triage test.

We used Stata 13.1 to analyse the data.

Disclosure

All the authors declared no competing interests.

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Tables and Figures:

Table 1: Baseline characteristics of the Swiss ADPKD Study

Variable	Baseline Visit	Number of patients
Age (yr; median [IQR])	32.91 (26.64-39.64)	N=204
Height (cm; median [IQR])	176 (169-182)	N=204
Weight (kg; median [IQR])	74.6 (64-86)	N=204
TKV (mL; median [IQR])	857.62 (565.86-1354.83)	N=204
eGFR (mL/min/1.73 m2, median [IQR])	82.78 (72.30 - 96.08)	N=204
Blood pressure systolic (mm/Hg; median [IQR])	131.25 (123-142.5)	N=204
Blood pressure diastolic (mm/Hg; median [IQR])	85 (76.75-91.75)	N=204
Blood Hamoglobin (g/dl; median [IQR])	14.1 (13.2-15)	N=199
Blood Urea (mmol/L; median [IQR])	5.4 (4.5-6.65)	N=200
Blood HDL (mmol/L; median [IQR])	1.39 (1.17-1.71)	N=199
Blood Cholesterol (mmol/L; median [IQR])	4.5 (4 - 5.2)	N=200
Blood Sodium (mmol/L median [IQR])	141 (139-142)	N=203
Male gender (%)	56.86 (116)	N=204
Hypertension (%)	64.22 (131)	N=204
Regular coffee consumption (%)	84.8 (173)	N=204
Symptoms (%)	60.29 (123)	N=204

Table 2: Basic Model and more extended model for estimating TKV (N=204)

Parameter	**Basic model**		**Extended model**	
	Coefficient	P Value	Coefficient	P-Value
Intercept	6.401646	0.000	11.09414	0.000
age	0.0039959	0.307	0.0033449	0.434
height	0.0020876	0.675	0.001101	0.834
egfr	-0.0119388	0.00	-0.0104033	0.000
weight	0.0061239	0.027	0.0055365	0.056
sex	-0.136016	0.160	-0.1628024	0.133
hypertension	0.2434446	0.002	0.0044227	0.020
coffee	0.1902784	0.040	0.2060419	0.008
symptoms	0.2124064	0.002	0.2455577	0.006
blood pressure dia			0.1888329	0.237
sodium			-0.0321973	0.059
cholesterol			-0.1058601	0.003
hdl			-0.0540799	0.542
urea			0.0246082	0.202

Table 3: Comparison of the basic and more extended model performance for TKV

Model	Mean difference between x and y	R^2	Correlation	IQR	RMSE	95% Limits of agreement	% within 30%
Basic model	103.894 (CI 28.342-179.446)	0.47	0.6923	332.643-3328.183	0.45	-990.680 - 1198.467	52.45
Extended model	92.553 (CI 16.903-168.202)	0.52	0.7199	316.927-3357.732	0.43	-989.764-1174.869	55.73

Table 4: Diagnostic accuracy of the first triage test and second test for the basic model and the more extended model

Triage Test for	TKV threshold	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Basic model (N=204)	750 mL	0.83 (0.77-0.88)	82.5 (74.2.88.9)	64.4 (53.7-74.3)	74.6 (66.1-81.9)	74.4 (63.2-83.6)
Basic model (N=204)	675 mL		88.6 (81.3-93.8)	53.1 (42.5-63.9)	70.6 (62.4-77.9)	78.7 (66.3-88.1)
Extended model (N=199)	750 mL	0.85 (0.79-0.90)	85.5 (77.5-91.5)	64.0 (53.2-73.9)	74.6 (66.1-81.9)	78.1 (66.9-86.9)
Extended model (N=199)	675 mL		91.8 (85.0-96.2)	55.1 (44.1-65.6)	71.6 (63.4-78.9)	84.5 (72.6-92.7)
Second test for	**TKV threshold**	**AUC (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Basic model (N=63)	750 mL	0.87 (0.77-0.96)	52.6 (28.9-75.6)	95.7 (85.2-99.5)	83.3 (51.6-97.9)	83.0 (70.2-91.9)
Basic model (N=58)	675 mL	0.87 (0.77-0.97)	64.3 (35.1-87.2)	90.9 (78.3-97.5)	62.9 (38.2-90.9)	88.9 (75.9-96.3)
Extended model (N=65)	750 mL	0.85 (0.76-0.95)	52.9 (27.8-77)	95.9 (85.2-99.5)	81.8 (48.2-97.7)	84.6 (71.9-93.1)
Extended model (N=51)	675 mL	0.88 (0.77-0.98)	54.5 (23.4-83.3)	92.5 (79.6-98.4)	66.7 (29.6-92.5)	88.1 (74.4-96.1)

Figure 1: Receiver operating characteristic curve compared the discriminating ability of the basic (grey) and extended (black) triage tests for estimating TKV with threshold of 750 mL(dot) and TKV of 675mL (triangle)

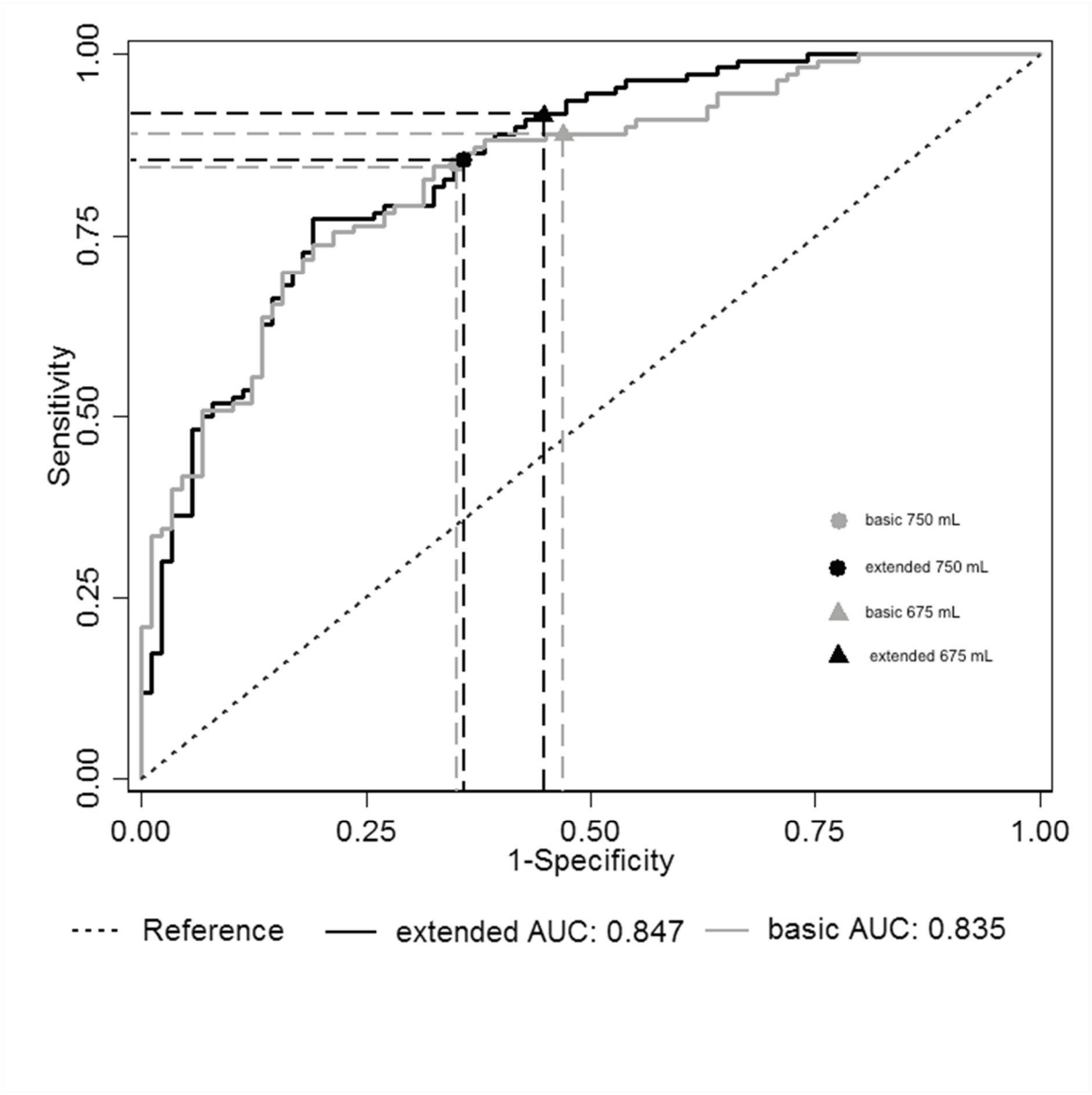
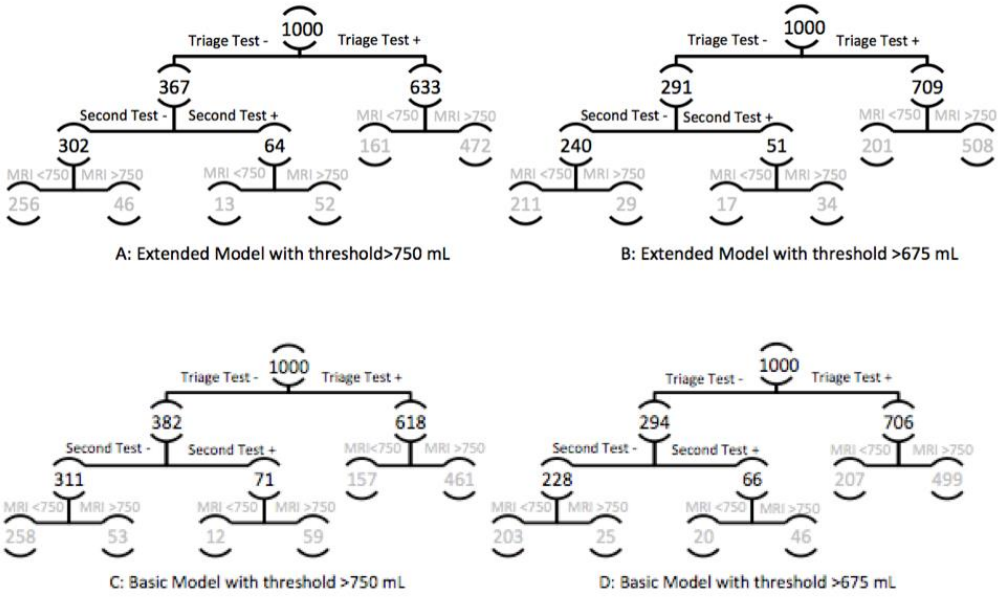


Figure 2: Expected clinical decisions based on triage tools

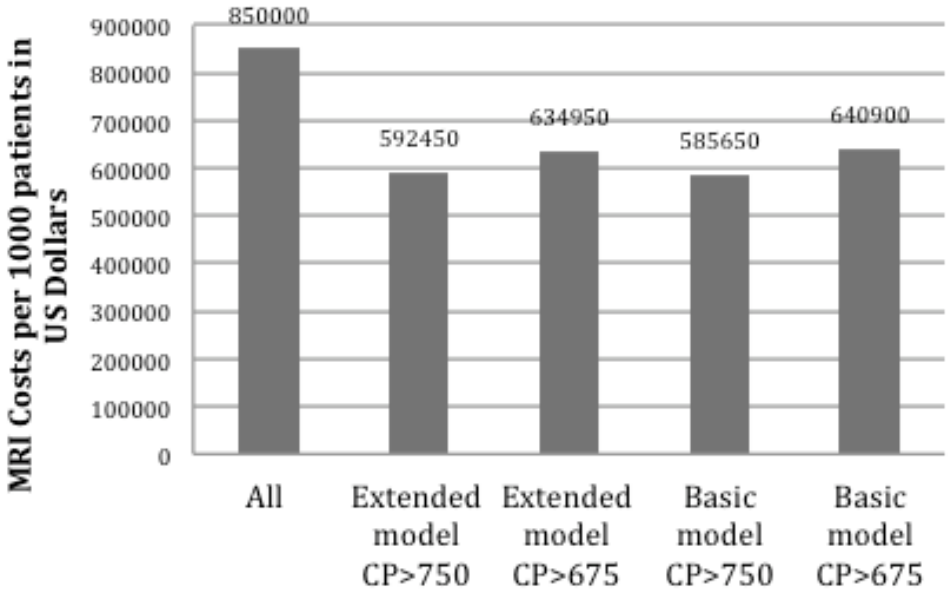


Caption

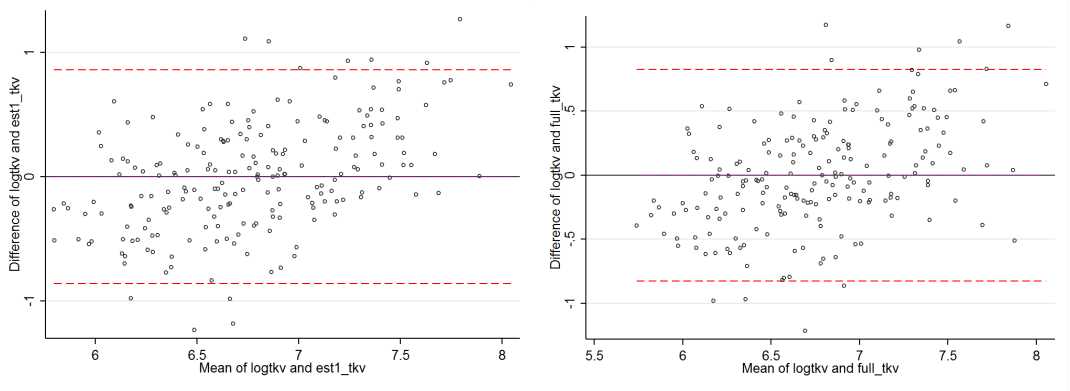
Triage tests for Total Kidney Volume-based management decisions (A,B: more extended and C,D: basic model) and a second test after 1 to 2 years per 1000 patients for the TKV threshold of 750 mL and TKV of 675mL.

Grey: results of the MRI examination

Figure 3: Expected MRI Costs per 1000 patients in a 2-year period (Assumption MRI costs 850$ per measurement)



Supplemental Figure 1: Performance of the more extended model and the basic model in estimating measured TKV



Caption:

A: Bland-Altman analysis of the measured TKV using MRI versus the estimated TKV derived from the basic model. B: Bland-Altman analysis of the measured TKV using MRI versus the estimated TKV derived from the more extended model.

Supplemental Table 1: Second test model for estimating TKV (R^2 = 43%)

Parameter	Basic model	
	Coefficient (SE?)	P Value
Intercept	5.646692	0.000
age	-0.0047606	0.552
egfr	-0.0081697	0.049
weight	0.0068691	0.188
sex	0.1734301	0.239
hypertension	0.3275095	0.016
coffee	0.1405864	0.208
flank pain	0.1858724	0.137
macrohematuria	0.5008101	0.092
bps	0.0088454	0.192
bpd	-0.0042365	0.633

Chapter IV

Temporal and geographical external validation study and extension of the Mayo Clinic Prediction Model to predict eGFR in the younger population of Swiss ADPKD Patients

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Provisorily accepted, pending final decision: BMC Nephrology

Abstract:

Background:

Prediction models in autosomal dominant polycystic kidney disease (ADPKD) are useful in clinical settings to identify patients with greater risk of a rapid disease progression in whom a treatment may have more benefits than harms. Mayo Clinic investigators developed a risk prediction tool for ADPKD patients using a single kidney value. Our aim was to perform an independent geographical and temporal external validation as well as evaluate the potential for improving the predictive performance by including additional information on total kidney volume.

Methods:

We used data from the on-going Swiss ADPKD study from 2006 to 2016. The main analysis included a sample size of 214 patients with Typical ADPKD (Class 1). We evaluated the Mayo Clinic model performance calibration and discrimination in our external sample and assessed whether predictive performance could be improved through the addition of subsequent kidney volume measurements beyond the baseline assessment.

Results:

The calibration of both versions of the Mayo Clinic prediction model using continuous Height adjusted total kidney volume (HtTKV) and using risk subclasses was good, with R^2 of 78% and 70%, respectively. Accuracy was also good with 91.5% and 88.7 % of the predicted within 30% of the observed, respectively. Additional information regarding kidney volume did not substantially improve the model performance.

Conclusion:

The Mayo Clinic prediction models are generalizable to other clinical settings and provide an accurate tool based on available predictors to identify patients at high risk for rapid disease progression.

Keywords: ADPKD, disease progression, epidemiology, kidney volume, prediction model, validation study

Background:

Prediction models in autosomal dominant polycystic kidney disease (ADPKD) are used in clinical settings for several purposes. They can inform patients about their prognosis. They can identify patients at greatest risk of rapid disease progression who might benefit most from new therapies. They can also identify patients with slower disease progression who might benefit from a care strategy that delays treatment until a later stage [1, 2]. Finally, prediction models are useful for identifying patients with a particular disease risk profile who would be suitable for clinical trials [2, 3]. Relevant outcomes for ADPKD prediction models include total kidney volume (TKV) and estimated glomerular filtration rate (eGFR)[4], the primary clinical indicators of disease progression. Established predictors of these outcomes include age, sex, earlier measures of TKV and eGFR and Polycystic Kidney Disease genotype[5, 6].

The vasopressin V2 receptor antagonist, tolvaptan, has been recently approved for the treatment of ADPKD but, due to notable side effects and expense, represents a treatment where good risk prediction is important for targeting use. Tolvaptan is the first approved drug shown to directly affect disease progression [7]; all other therapies target co-morbidities that may contribute to progression but do not affect the underlying disease [8]. The indication for tolvaptan is currently limited to patients with evidence of rapid progression in Switzerland and European Union according to the European Medicines Agency [9] where the expected benefit outweighs the risk of side effects and associated high treatment costs [10]. The

challenge for clinicians is to identify patients at highest risk of rapid progression without extensive diagnostic screening across the full patient population. Currently, TKV and the rate of TKV change are considered the most accurate predictors of progression [11]. However, for routine clinical and research purposes, direct measurement of kidney volume is less feasible due to time and technical demands as well as expense.

Recently, Mayo Clinic investigators developed a risk classification system for ADPKD patients using a single TKV value and an accompanying prediction model [12, 13]. In 2016, the ERA-EDTA Working Group published a recommendation that the Mayo Clinic prediction model be used to discriminate patients at high risk for rapid disease progression [14]. However, the prognostic performance of the prediction model has yet to be evaluated in an external sample outside the US, which is critical for establishing accuracy and generalizability of risk discrimination across different patient populations [12].

The aim of our study was to externally validate the Mayo Clinic Model using data from the prospective longitudinal Swiss ADPKD study, with a patient population both geographically and temporally removed from the original patient population in which the model was developed. We also sought to evaluate whether improved prediction performance could be achieved by including additional measurements of the most relevant predictor: height adjusted total kidney volume (HtTKV).

Methods

Swiss ADPKD Validation data

Participants were eligible for the Swiss ADPKD study if they had an ADPKD diagnosis, were over 18 years of age and had an eGFR over 30 ml per min per 1.73m^2 at enrolment [15]. For the present analysis, participants from the Swiss ADPKD study were

included if they were under active follow-up between 2006 to 2016, had at least one follow-up visit and had not been treated with tolvaptan. Approximately 3% (N=6) of patients had Atypical ADPKD (Class 2) and were excluded from the present analysis. Visits were done at the university hospital in Zurich and at the Hirslanden hospital Zurich. At every scheduled clinical visit, data were collected on medical history, kidney imaging metrics and laboratory values from blood and urine samples. Clinical measurements and assays were done according to a protocol with standardized operating procedures [16, 17]. Following an initial visit, a second visit occurred within 6-12 months and then visits were scheduled annually; when a study participant missed a scheduled visit, a study visit occurred at the next available opportunity to collect MRI and other study data. The local ethics committee in Zurich approved the study (EK-number 1178) and all patients provided written informed consent.

Mayo Clinic risk classes and eGFR prediction model

The Mayo Clinic prediction model has been described [12]. Briefly, five risk subclasses with theoretical yearly percentage increases in kidney volume of <1.5% (Class 1A), 1.5-3% (Class 1B), 3-4.5% (Class 1C), 4.5-6% (Class 1D) and >6% (Class1E) were defined based on age and imaging data (Figure 1) [12]. Then a linear mixed-effect model was used to predict eGFR after t years of follow-up using baseline ($t = 0$) predictors: $\log_2$HtTKV or risk subclass group (1A-1E) [12], sex, age, eGFR from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. Years of follow-up was included as a linear term with a subject specific random effect. Interaction terms of years of follow-up with all predictors were also included in the model.

Outcome

Estimated Glomerular Filtration Rate (eGFR)

In accordance with the Mayo Clinic model, our primary outcome was eGFR at *t* years follow-up. Serum creatinine was measured at each visit by the central laboratory institute of clinical chemistry of the university hospital and the central laboratory in Zurich using the modified Jaffé method traceable to an isotope-dilution mass spectroscopy reference [17]. eGFR at baseline ($t = 0$) was estimated using the CKD-EPI equation [18].

Predictors

Total Kidney Volume (TKV)

At every study visit, a measurement of kidney volume was taken by using a standardized procedure protocol for the Magnetic Resonance Imaging (MRI)[16]. MRI acquisitions contain a breath-hold T1-weighted fast spoiled gradient echo sequence without fat suppression sequence (4 mm slice thicknesses) and trans-axial T2 weighted fast spin echo sequences. TKV was estimated by hand contouring [16]. Height adjusted total kidney volume (HtTKV) was obtained by dividing TKV by patient height (ml/m).

Statistical methods

Baseline characteristics are given as proportions and medians (interquartile range). Patients were stratified into the five subclasses (1A-1E) based on the Mayo Clinic estimated kidney growth rates limits of 1.5%, 3.0%, 4.5% and 6% (Figure 1).

We applied the Mayo Clinic model to all participants of the Swiss ADPKD study to predict eGFR at *t* years follow-up, using $\log_2$HtTKV as a continuous predictor and keeping regression coefficients fixed at the values determined from the Mayo Clinic development

sample. We also applied a second Mayo Clinic model, that replaced the baseline (t = 0) $\log_2$HtTKV with baseline risk subclass (1A-1E).

To try to improve upon the Mayo equation predictive performance, we tested two modifications to the original Mayo model. First, we included in the model a second HtTKV follow-up measurement (mostly within 6-12 month of the baseline measurement) to provide additional information on individual change in TKV (Model 1). The regression coefficient for the HtTKV term was refit to the Swiss ADPKD study sample, but all other regression coefficients were kept fixed at their original value, including the intercept. Second, we included information on all subsequent and available HtTKV measurements, again refitting the regression coefficient for the HtTKV term while keeping all other regression coefficients fixed at their original Mayo Clinic values (Model 2). Updated models with and without interaction terms of HtTKV*years were evaluated.

Evaluation of model performance

The model fit to the validation data set was assessed using R-squared statistics and Akaike's information criterion (AIC). Discrimination was visually assessed using scatter plots comparing observed and predicted eGFR values with an estimated regression line, line of equality and confidence interval. The agreement was assessed using the Bland-Altman analysis [19]. We followed Steyerberg's approach to validate and update clinical prediction models [10].

To compare the performance of the prediction models we estimated the continuous ranked probability score (CRPS) of the 3 competing models: original model, updated model 1 and updated model 2. The CRPS is a proper scoring rule to assess univariate predictive distributions with smaller values indicating better predictive performance [20]. The metric

takes into account the entire predictive distribution of the outcome [21] and assesses both calibration and precision of predictive distribution. For evaluation of models with added TKV information, five-fold cross-validation was used given that no external validation was available [10].

The predictor HtTKV was missing in 3% of the participant-visits. We used multiple imputation (MI) to impute the missing values; specifically, a Markov Chain Monte Carlo method was implemented and multivariate normality was assumed [22]. We generated 30 imputed data sets for each model with HtTKV [23].

Stata 13.1 was used for all data analysis and graphics.

Results

Characteristics of the Swiss ADPKD study sample

Between April 2006 and March 2016, 214 patients with an ADPKD diagnosis were enrolled in the Swiss ADPKD study, contributing a total of 1985 person-visits. At baseline, the median age was 34 years (interquartile range [IQR]: 27-40), the median eGFR was 82 ml/min per 1.73 m2 (IQR: 70-95) and the median HtTKV was 497 ml/m (IQR: 317-762). Swiss ADPKD study follow-up times ranged from a minimum of 0.42 years for new enrolees to a maximum time of 10.28 years. We assessed change from one class to another in 206 patients from the 214 swiss ADPKD class1 patients. In total, there were 52 patients (25%) from the 206 Swiss ADPKD Study participants who progressed to a more severe risk class over the median 5 year follow-up and 7 (3%) who changed to a milder disease risk class. More than the half of the patients in class 1A (56%) remained in their class: 40% (10 patients) progressed from 1A to 1B (1 patient from 1A to 1C), 18% (9 patients) progressed

from 1B to 1C (1 patients from 1B to 1D), 28% (16 patients) progressed from 1C to 1D (4 patients from 1C to 1B) and 28% (15 patients) progressed from 1D to 1E (3 patients from 1D to 1C).

Comparison of the Swiss ADPKD study sample to the Mayo development sample

Compared to the Mayo clinic development sample of 376 patients, the average eGFR was higher by 11 ml/min per 1.73 m^2, median age was 10 years younger, and median HtTKV was 155 ml/m lower in the Swiss ADPKD study patients. Swiss ADPKD patients had a median follow-up time of 5 years (IQR: 2 to 9 years) compared to 6 years (IQR 4-10) in the Mayo Clinic patients. Comparing progression rates, more patients progressed in the Swiss ADPKD Study at 24% across all initial risk classes compared to 11% to 16% in the Mayo clinic development sample, though the median follow-up was 5 years compared to 4 years in the Mayo Clinic.

External Validation of the Mayo Clinic Model

In the Swiss ADPKD patient group, the Mayo Clinic model with the predictor log_2HtTKV performed well with explained variance (R^2) of 78 % (Table 2), compared to the R^2 of 69% in the development data set. Replacing baseline TKV with risk subclasses in the model resulted in a poorer model fit with a R^2 of 70 %, which is slightly lower to the R^2 of 72 % noted in the development set.

The scatter plot of observed eGFR versus predicted eGFR indicated good discrimination with 91.5% of the predicted within 30% of the observed when log_2HtTKV was included as a continuous predictor (Figure 2A, table 1) and 88.7 % of the predicted within 30% of the observed when risk subclasses were included (Figure 2B, table 2). The

Bland-Altman analysis shown in Figure 3 indicated a lower bias for the log_2HtTKV model and little distortion of the variability of the distribution, as seen from the approximate zero slope of the regression line.

Improving the Mayo prediction model

To evaluate whether the Mayo prediction model performance could be improved if additional information on TKV was available, we modified the formula to include subsequently TKV measurements. Updated model 1 (number of observation= 1867), which included a follow-up TKV measurement, showed good overall performance with a R^2 of 77%, an AIC of 13557.91 and CRPS of 58.16 (Table 2). In updated model 2 (number of observation= 1344), which included all available follow-up TKV measurements, resulted in a slightly better CRPS of 57.24 and substantially improved AIC of 9706.15 compared to Model 1. The R^2 was reasonably similar between the updated models and similar to the original Mayo Clinic model. Good agreement between observed and predicted was maintained as shown by the high correlation (Figure 2C, 2D). Both updating models reduced the bias and provided a good fit to the data (Figure 3C, 3D). An interaction term of TKV*years in the updated models did change performance (Table 2).

Discussion

Accurate risk prediction is important for guiding clinical care, particularly when there are substantial costs to treatment. The goal of the Mayo Clinic model was to provide risk prediction for the ADPKD patient population; however prognostic performance has never been established in a broader patient sample and external validity of a prediction model is critical to assure accurate prediction across patient populations and therefore establish the model's utility as a clinical tool.

Our results indicated that the Mayo Clinic model performs well in our Swiss ADPKD patient sample. Both models showed adequate discrimination and good calibration. The overall prediction performance in our sample as assessed with R^2 was higher when the continuous predictor HtTKV was the used than when risk subclasses were used. These results suggest the models are generalizable and would perform well in routine clinical settings. Given the higher eGFRs in the Swiss ADPKD Study, these results were particularly notable, as poorer performance might be expected with upward shifts in the distribution of eGFR compared to the development set. However it should be noted that in the original Mayo Clinic prediction model and in our validation, an estimated eGFR from the CKD-Epi formula was used for the baseline assessment of kidney function. This estimation may itself introduce bias in the prediction of later kidney function, relative to the true GFR. To the extent that the CKD-Epi formula may perform differently in the two cohorts, our results could have impacted. We also did not distinguish between polycystic kidney disease genotypes 1 and 2, and prediction performance could vary between these groups. Further the R^2 is known to be sensitive to the range and variability of the data; thus apparent improvement in prediction performance based on a higher R^2 in our validation cohort compared to the original development cohort should be interpreted with caution.

It should be noted that the Mayo Clinic prediction model development set used TKV assessed via the ellipsoid equation [12], while the present study used the gold standard TKV assessment by boundary method [24], which could introduce additional variability in prediction performance. However, a recent study assessed patient reclassified by the Mayo risk classification system resulting from these different TKV assessment method. The

investigators found only a limited impact with a few patients reclassified mostly to lower risk categories [24].

A second aim of our study was to evaluate whether additional information regarding TKV change could improve the model prediction performance. Based on the results of the validation study and relatively large size of the development sample, we followed Steyerberg's approach [25] and fixed all regression coefficients at their original values under the premise that re-estimation runs the risk of replacing reliable but modestly biased estimators with unbiased but unreliable ones [10]. Allowing only the coefficient for TKV to vary, we found that the R^2 remained relatively unchanged when baseline TKV was replaced with measurements from the first two assessments. Further including all available TKV measurements, including a current TKV assessment, did not provide substantial improvement in the prediction performance that would justify the additional cost, time and effort of TKV measurement.

Strengths of our study include a patient population that was entirely independent of the Mayo Clinic data set, varying geographically, culturally and temporally from the original development cohort. In addition the Swiss ADPKD study has comprehensive follow-up with repeated measurements of kidney volume over time in a well-described cohort of untreated ADPKD patients at an early disease stage. The inclusion of recently enrolled patients as well as those with nearly 10 years of follow-up establishes generalizability across the patient population. Prediction models need to perform well in general ADPKD patient populations, as they are used for clinical decision-making.

Conclusions:

In conclusion, we found that the Mayo Clinic prediction model is an accurate tool to identify those at highest risk for rapid disease progression as defined by declining kidney function. The performance of the model was not substantially improved with by including additional TKV assessments, suggesting that follow-up TKV measurements may not be worth the cost and burden for the purposes of predicting progression. The Mayo prediction model may be a valuable tool for identifying patients for whom new treatments such as tolvaptan will provide benefits that outweigh the burden of side effects.

Abbreviations

ADPKD: Autosomal dominant polycystic kidney disease **TKV**: total kidney volume **eGFR:** estimated glomerular filtration rate **HtTKV:** height adjusted total kidney volume **CRPS:** continuous ranked probability score **MRI:** Magnetic Resonance Imaging **AIC:** Akaike's information criterion **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration

Declarations

Availability of data and materials

All data underlying the findings are within the paper or available upon reasonable request from the corresponding author.

Authorsô contributions

All authors made substantial contributions to the scientific process of this study resulting in preparation of this paper. LGR, JB, MAP and ALS did the conception design. LGR, JB, MAP, ALS and AGA had full access to all data, contributed to the analysis and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the data and participated in discussions related to interpretation. LGR wrote the first draft of the manuscript. All authors contributed to drafting or editing the manuscript and approved the final draft.

Competing interests

The authors declare that they have no competing interests.

Consent to publication

Not applicable.

Ethics, consent and permissions

Ethics approval and consent was given by the local ethic committee (Ethics committee in Zürich, EK-number 1178). Written informed consent was obtained from all patients.

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Tables and Figures:

Table 1: Baseline characteristics of the development set from the Mayo Clinic and the validation set from the Swiss ADPKD Study

Class	Total number # (%)	Men/Women(n/n)	Median Age (yr)	Median eGFR (ml/min per 1.73 m2)	Median HtTKV (mL/m)	Median Follow-Up (yr)
Mayo Clinic						
1A	40 (10.6)	7/33	50(44-58)	84(64-97)	249(214-280)	5 (3-10)
1B	88 (23.4)	23/65	46(36-53)	78(62-97)	433(322-565)	6(3-9)
1C	122 (32.4)	46/76	44(36-50)	71(47-98)	701(514-1037)	6 (4-10)
1D	77 (20.4)	40/37	41(34-49)	60(36-96)	1195(843-1544)	6 (4-11)
1E	49 (13.0)	28/21	36(29-43)	46(26-94)	1874 (1118-2609)	5 (3-8)
Subtotal	376 (100)	144/232	44(35-51)	71(44-97)	651 (431-1195)	6 (4-10)
Swiss ADPKD						
1A	27 (12.6)	9/18	29.43 (24-37)	86.67 (78-102)	199.52 (178-232)	5.19 (1.99-8.35)
1B	52 (24.3)	20/32	36.15 (29-46)	83.84 (72-100)	343.75 (272-421)	5.28 (3.13-7.92)
1C	60 (28.0)	35/25	35.56 (28-41)	83.14 (71-92)	514.31 (407-630)	4.24 (2.02-8.26)
1D	52 (24.3)	38/14	32.48 (28-38)	79.35 (72-94)	705.70 (579-910)	6.25 (2.85-8.95)
1E	23 (10.7)	18/5	29.82 (23-35)	70.30 (56-86)	1166.50 (920-1425)	6.93 (3.27-8.53)
Subtotal	214 (100)	120/94	34.22 (27-40)	82.20 (70-95)	496.58 (317-762)	5.13 (2.21-8.48)

Table 2: Predictive performance of the validation, the updated models and the sensitivity analysis (in grey)

	R^2	Bias	95% Limits of Agreement	Correlation	% within 30 %	AIC	CRPS
Validation model: risk class (1985 observations)	0.7039	5.29	-16.8,27.3	0.839	88.7	-	-
Validation model: TKV (1985 observations)	0.7853	-2.73	-20.4,15.0	0.871	91.5	14386.98	73.36
Updated model 1: 2 TKV's (1867 observations)	0.7704	0.42	-17.4,18.3	0.872	96.6	13557.91	58.16
Updated model 1 with interaction term	0.7720	0.82	-16.9,18.6	0.879	96.6	1322.3	81.85
Updated model 2: TKV time-varying (1344 observations)	0.7989	0.34	-17.1,17.8	0.889	96.1	9706.15	57.24
Updated model 2 with interaction term	0.8015	0.57	-16.8,17.9	0.895	96.1	9715.05	83.39

Figure 1: Subclassification of ADPKD patients based on HtTKV limits on their age at baseline. Limits are defined from the Mayo Clinic based on estimated kidney growth rates of <1.5% (dark green), 1.5-3.0% (mint), 3-4.5% (yellow), 4.5- 6% (orange) and >6%(red).

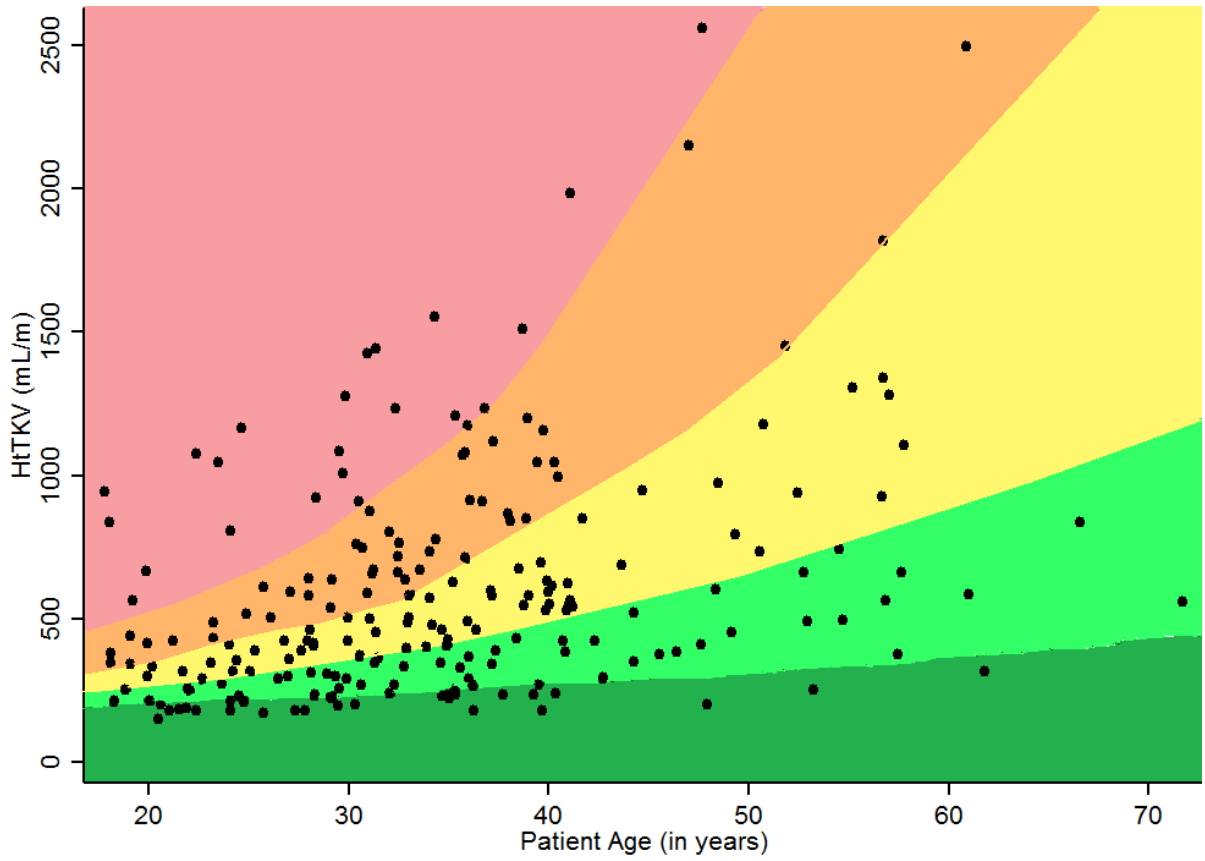


Figure 2: 2A: Scatterplot of the observed eGFR versus the predicted eGFR derived from the model obtained from the development set with TKV as predictor with regression line and the line of equality. 2B: Scatterplot observed eGFR vs. predicted eGFR derived from the model obtained from the development set with the five subclasses as predictor. 2C: Scatterplot of the observed eGFR versus the predicted eGFR derived from the updated model 1 with two TKV measurements and 2D: updated model 2 with time-varying TKV.

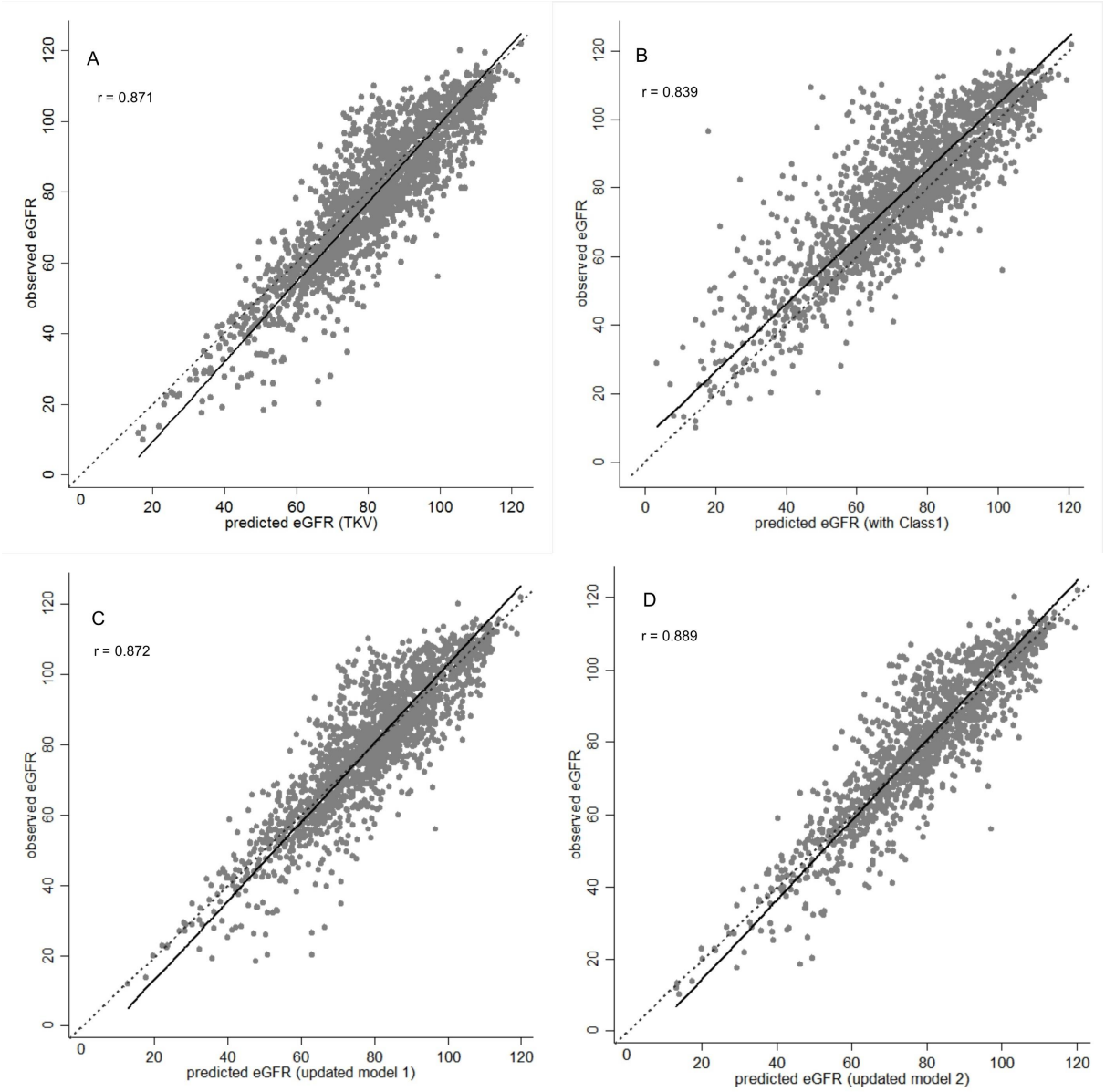
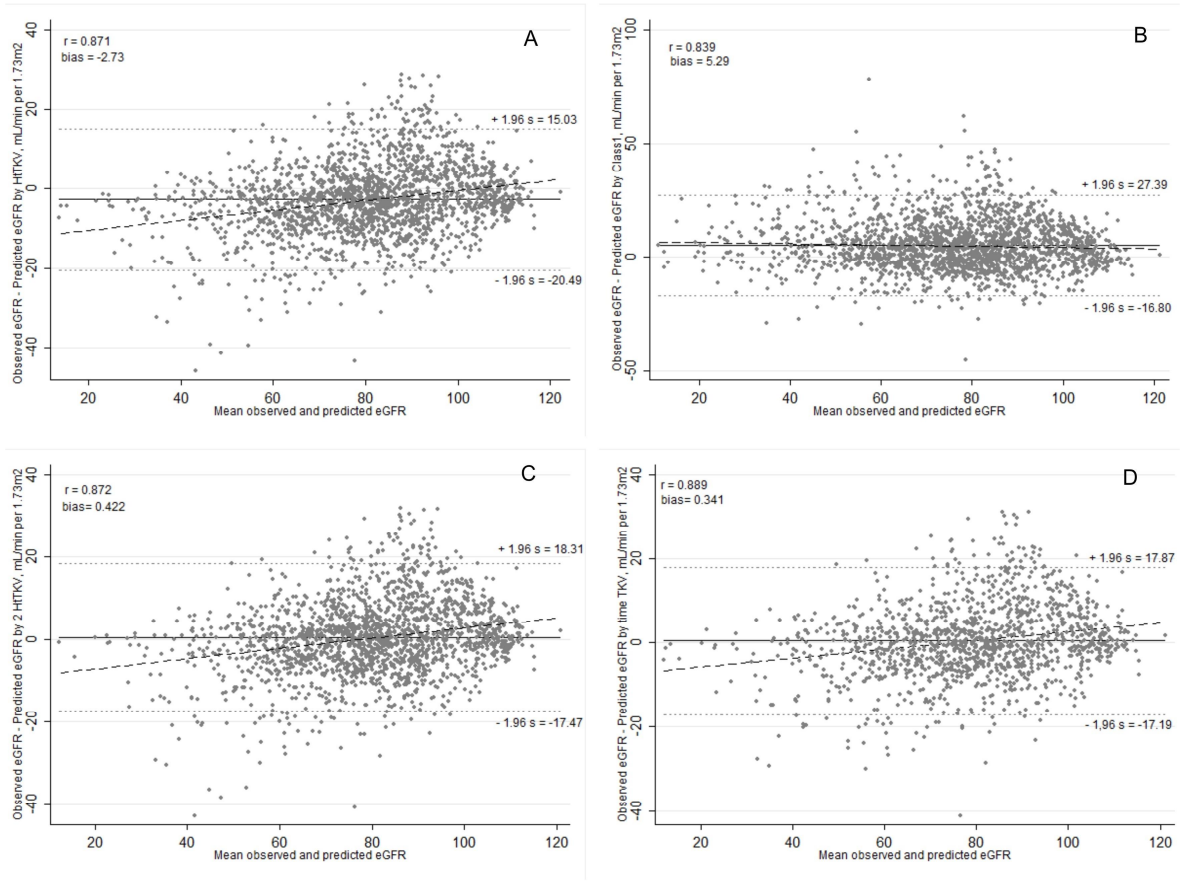


Figure 3: 3A: Bland-Altman analysis of the observed eGFR versus the predicted eGFR derived from the model obtained from the development set with TKV as predictor. 3B: Bland-Altman analysis observed eGFR vs. predicted eGFR derived from the model obtained from the development set with the five subclasses as predictor. 3C: Bland-Altman analysis of the observed eGFR versus the predicted eGFR derived from the updated model 1 with two TKV measurements and 3D: updated model 2 with time-varying TKV



Chapter V

General Discussion

The following discussion summarizes the main findings of this thesis and puts them into a broader context of ADPKD research and evidence-based management. The first paper of the thesis contributes to the non-pharmacological management of ADPKD patients. The second and third articles support evidence-based management in a clinical setting of expensive diagnostic tests and the selection of non-drug and drug treatments through prediction models.

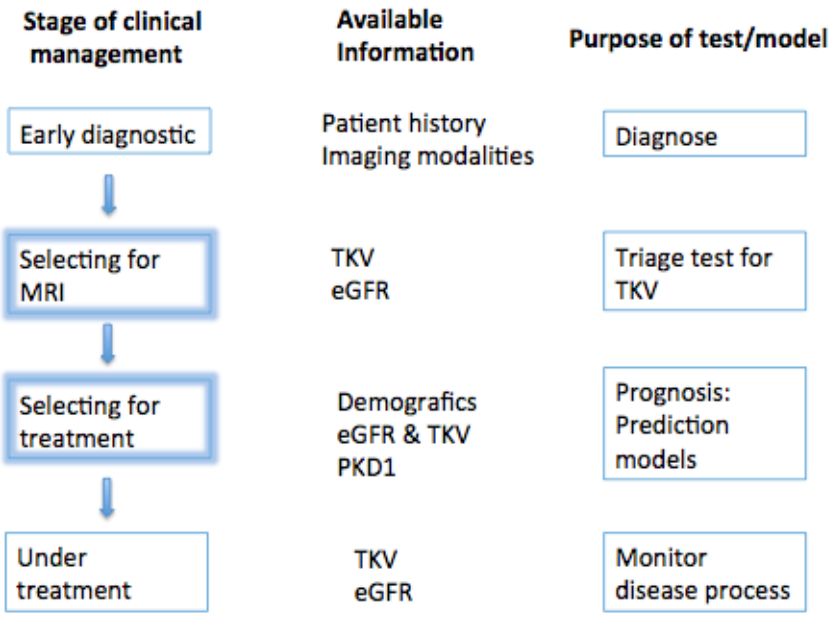
Implication for evidence-based management in clinical practice

In the management of patients with ADPKD, non-medical interventions such as lifestyle factors are important for the control of the disease progression and hypertension. Avoiding high sodium/salt intake, avoiding smoking, lowering alcohol intake, reducing coffee intake, exercising, staying hydrated and maintaining a healthy diet are important lifestyle factors for ADPKD patients. Lifestyle factors are relevant for ADPKD patients to reduce risk factors and strengthen resources with the aim to prolong and stabilize renal function until renal replacement therapy (RRT) is required. Therefore, avoiding potential risk factors such as coffee has been recommended to delay disease progression. Our first study is the first prospective cohort study that assessed the association between coffee consumption and disease progression. The lack of an association suggests that a recommendation against coffee consumption may not be justified.

In clinical practice, the clinical diagnosis of ADPKD in patients with positive family history is confirmed when the number of cyst meet the Pei-Ravine diagnostic criteria [1, 2]. In the later stage of clinical management when the decision for risk-stratified treatment is needed or patients are under treatment, the purpose of a test is to provide prognostic

information or monitor disease progress. Here, our triage test and the validated prediction model can be implemented easily (Figure 1).

Figure 1: Use of a test/model in clinical ADPKD practice for diagnosis and prognosis (highlight the new triage test and the validation of the prediction model).



Our triage test, presented in Chapter III, can be used in clinical practice to inform patients about their expected TKV and help clinicians to reduce the number of MRI tests that are not necessary in patients who will not be eligible for treatment. The high sensitivity of our triage test suggests that clinicians can identify such patients accurately and safe resources and cost. Since all variables of the triage test are readily available, clinicians can use the triage test in their daily practice. The implication of a clinical decision-making tool for triaging patients towards or away from an MRI could also form the basis of a reimbursement policy, because MRIs are still not reimbursed in some countries. In particular, patients in less developed countries could benefit from a more efficient allocation of MRI resources in clinical practice.

Accurate and feasible risk prognosis is essential for guiding clinical care, particularly when patients must be selected wisely for a drug. Our independent geographical and temporal external validation of the two Mayo Clinic models suggests that these models are generalizable in clinical settings and that they are accurate tools that use easily available predictors for identifying patients at high risk for rapid disease progression. Selecting patients for Tolvaptan treatment is justified as there are substantial side effects associated with treatment and so patients receiving treatment should incur benefits that ourweigh the harms.

Implication for research

The longitudinal cohort study is used in epidemiologic research to investigate potential associations and answer questions regarding disease prognosis, in this thesis, whether or not a given factor such as coffee intake in patients with ADPKD influences the risk of an outcome. From a broad public health perspective, cohort studies have often reported a beneficial effect of coffee intake on various health outcomes and coffee consumption could have a protective effect on avoiding for example cancer, diabetes and heart disease [3-5]. Besides these results, other studies also showed a negative effect of coffee consumption on blood values such as blood pressure and cholesterol. A dose response meta-analysis of 21 cohort studies showed a non-linear association between coffee intake and mortality from all causes and cancer. The highest risk reductions were observed by drinking 4 cups per day; for all-cause mortality drinking coffee was not associated with higher mortality due to cancer [6]. In the context of the management of kidney disease, a community-based study showed that coffee consumption was associated with a lower risk of chronic kidney disease [7].

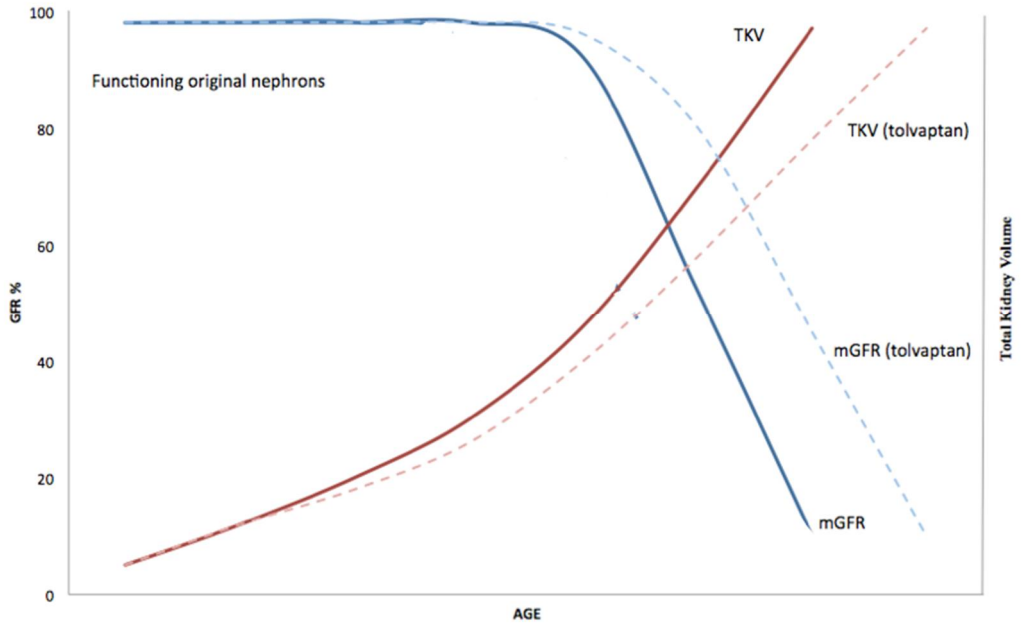
From an evidence-based management focus on ADPKD, the effects of caffeine have been insufficiently investigated to support a strong recommendation against caffeine consumption [8]. Our study is the first prospective cohort study that investigates the association between coffee consumption and disease progression in an ADPKD cohort and contributes a major step towards closing the reported gap in the research. However, following the approach of the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) Working Group, the current evidence base [9], which is now restricted to our study, would still be considered weak at best. Thus guideline developers may abstain from making any recommendations for or against coffee consumptions for patients with ADPKD and call for additional high-quality cohort studies or randomized controlled trials that assess the effects of coffee consumptions on disease progression.

Our triage test for TKV-based management decisions in ADPKD is the first test which aims to identify patients unlikely to meet the minimal TKV thresholds required for tolvaptan treatment and for whom TKV measurement via MRI can be avoided. For a reliable implementation of our triage test, external validation is needed. Ideally, other groups would assess the diagnostic accuracy of our triage tests and update the underlying models as appropriate. Also, future studies should assess if using a triage test truly changes decision making on imaging tests and if patients not undergoing MRI experience negative consequences such as undetected rapid progression. Ideally, randomized trials would compare the outcomes of ADPKD patients with different management pathways such as with or without the triage test [10]. Alongside such studies, the cost effectiveness of these management pathways should be assessed. Such studies would inform guidelines on ADPKD management but also policies on reimbursement of MRI and treatment cost.

There is still a need for a defined algorithm to assess indications for initiation of treatment in ADPKD. The clinical progression in ADPKD patients has a varying course till

ESRD. Several patients progress to ESRD at an early disease stage whereas others never reach ESRD [11]. Since patients with rapid progressive disease have the most benefit from aggressive treatment, prediction models that can identify them are important [12-14]. We validated the Mayo Clinic prediction models for the outcome eGFR and extended it by adding subsequent TKV measurements in our own ADPKD cohort. From an evidence-based management focus on ADPKD, the Mayo risk model for the outcome eGFR has been insufficiently evaluated regarding the initiation of treatment over a long-term perspective. For treatment initiation, it is necessary to consider many factors including adverse effects, lifestyle factors, contraindication and patient's incentive [12].

Figure 2: Correlation between GFR and TKV as a disease marker for ADPKD. Figure adapted and modified from [18]. Measured GFR (dark blue) is the % of function depending on age. It stays very long stable till late decline to ESRD. % of functioning original glomeruli (light blmue) decline before mGFR decline. TKV (red) is increasing with age. The dashed line is the expected development under a treatment with tolvaptan.



However, eGFR as an outcome may not be the optimal measure for selecting an ADPKD patient, because of its characteristic as a late disease marker. Kidney function remains stable for a long period and serum creatinine levels only rise once the kidneys have serious and irreversible damage (Figure 2). Considering intake of tolvaptan for a long time [15, 16], GFR decline could be retarded in the future, when patients start the treatment at an early age [17]. Change in TKV shows disease progression at an earlier stage and with greater precision than change in eGFR (Figure 2). Accurate TKV estimation equations are still limited and a future challenge is the development of prediction models with easily available markers for the outcome of TKV.

Conclusion

When put into the context of available evidence the three studies of this PhD thesis contribute to the major therapy goal of slowing down disease progression. Our results suggest that guideline developers may lift the recommendation to restrict coffee consumption in patients with ADPKD and make recommendations for or against coffee consumption only if more high-quality studies provide the evidence beneficial or harmful effects of coffee consumption. The triage tests and prediction models developed and validated here support patient and physician evidence-based decisions on the use of diagnostic imaging and on the indication of non-drug and drug therapies. Such tests are, however, only the beginning of developing evidence-based recommendations for testing and treatment pathways. The results of this thesis open the door for the judicious use of expensive imaging tests and novel treatments. But only a combination of additional primary studies such as randomized trials and of modelling studies for estimating benefits, harms and cost of testing and treatment pathways will ultimately inform clinical practice on the best management strategies that optimally balance benefits, harms and cost of patients with ADPKD**.**

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Appendix I:

Urinary Biomarkers at Early ADPKD Disease Stage

Katja Petzold, Diane Poster, Fabienne Krauer, Katharina Spanaus, Gustav Andreisek, Thi Dan Linh Nguyen-Kim, Ivana Pavik, Thien Anh Ho, Olivier Devuyst, Andreas L. Serra, Laura Rotar

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Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by a decline in renal function at late disease stage when large portion of functional renal parenchyma is replaced by cystic tissue. Thus, kidney function, assessed by estimated glomerular filtration rate (eGFR) does not well represent disease burden at the early disease stage. Here we investigated various urinary markers for tubular injury and their association with disease burden in ADPKD patients at early disease course.

Methods:

ADPKD patients between 18 and 40 years with an eGFR of 70 ml per min per 1.73m^2 and more were eligible for this cross-sectional study. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule 1 (KIM-1), and Uromodulin (UMOD) were investigated by Enzyme-linked immunosorbent assay. Clara Cell Protein 16 (CC16) was investigated using Latex Immuno Assay. Cryoscopy was performed to assess urine osmolality and urinary albumin creatinine ratio (UACR) was calculated. Multiple regression analysis was applied to evaluate the association and the predictive properties of biomarkers on eGFR and height adjusted total kidney volume (htTKV), incorporating different control variables for adjustment. Applying bootstrapping method internally validated results.

Results:

In 139 ADPKD patients (aged 31 ±7 years) with a mean eGFR of 93 ± 19 ml per min per 1.73 m^2 the total kidney volume was negatively associated with eGFR and UMOD and positive associated with age, UACR, KIM-1 and urine osmolality after adjustment for possible confounders. Urine osmolality and htTKV were also associated with eGFR, whereas we found no association of CC16, NGAL and UMOD with eGFR or htTKV.

Conclusion:

In ADPKD urine osmolality, UACR and KIM-1 are independently associated with kidney size but not with renal function. Urine osmolality was associated with eGFR following adjustment for multiple confounders. Our results indicate that the urinary biomarkers osmolality, UACR and KIM-1 have the property to assess disease state at early ADPKD stage.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited kidney diseases. It is characterized by a decline of glomerular filtration rate at late disease stage and inter- and intrafamilial variability in age of end stage renal disease (ESRD) onset, implying a challenge to predict individuals' disease progression. The development and continued accretion of cysts, as the most prominent feature in ADPKD, leads to a massive enlargement of the kidney and subsequently to a loss of its function. So far, no disease modifying treatment has been available, despite the recent approval of Tolvaptan in Japan, and only comorbidities, like hypertension, urinary tract infections, pain, and kidney stones can be treated. Due to hyperfiltration of the remaining nephrons kidney function stays stable over decades. Thus, traditional markers for kidney function like serum creatinine and estimated glomerular filtration rate (eGFR) have limited ability to accurately assess the disease state and to predict progression the early course of ADPKD. Increasing evidence suggests that total kidney volume qualifies as a marker for disease progression in ADPKD.[1] In fact, the disease state may be reflected more accurately by total kidney volume and kidney growth rate than renal functional parameters like eGFR or creatinine clearance.[2] Total kidney volume can be accurately assessed by magnetic resonance imaging (MRI). However MRI derived kidney volume measurements are time and cost intensive and this modality is not routine clinical practice and requires high technical expertise.

Renal cystogenesis in ADPKD is a complex process, characterized by abnormalities in tubular cell proliferation, fluid secretion, extracellular matrix formation, and cell polarity.[3] This results in an impaired filtration barrier, diminished tubular reabsorption, upregulation of tubular proteins and release of markers by recruited inflammatory cells, which can be detected in patients' urine.[4] Biomarkers are used to define the patients' state in a certain

disease condition, to predict prognosis, and to quantify the effect of a pharmacological approach. Mayeux et al defined two major types of biomarker. Biomarkers of disease that are used in the diagnosis, treatment and prognosis of a disease and biomarkers of risk exposure.[5] Type 0 biomarkers (diagnostic biomarkers) are markers reflecting the natural history correlating with clinical indices whereas biomarkers of type 1 (predictive biomarkers) capture the effect of an intervention.[6] Type 0 biomarkers, reflecting tubular damage, that have been investigated in various settings of kidney disease and may be of interest in ADPKD are Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule 1 (KIM-1), Uromodulin (UMOD), Clara Cell Protein 16 (CC16) and albuminuria.[6] NGAL has been extensively investigated as a biomarker, due to its rapid increase in different settings like acute kidney injury, cardiac surgery, and kidney transplantation.[7-11] KIM-1 does not occur in human urine under physiological conditions and has been described as progression marker in kidney disease.[2] UMOD, the most abundant protein in human urine, regulates tubular function and shows protective properties against uropathogenic E. coli and the formation of kidney stones. [12] Decreasing levels of urinary UMOD have been reported in various settings of chronic kidney disease (CKD), like glomerulonephritis, diabetic nephropathy or tubulointerstitial nephropathy.[12-15] Urinary CC16 is consistently associated with defective endocytic uptake by the proximal tubule. It has been shown that CC16 levels are increased in patients with diabetic and HIV-induced nephropathy, as well as in renal Fanconi syndrome.[16,17] There is an unmet need to discover new biomarkers that allow an easy and non-invasively assessment of ADPKD disease state. We investigated the potential properties of the aforementioned markers for assessing disease state by evaluating their association with kidney volume and renal function in patients at early stage of ADPKD.

Methods

Study Subjects

Subjects were eligible for enrolment if they belong to the well-described SUISSE ADPKD cohort.[18,19] Male and female patients with proven ADPKD diagnosis, examined by kidney ultrasonography, according to Ravine criteria, and a positive family history were eligible when aged between 18 and 40 and presenting with an eGFR of 70 ml per min per 1.73m^2 and above as shown in Table 1.[20] In patients with negative family history, proof of a mutation in the *PKD1* or *PKD2* genes was required for enrolment (sequencing analysis by Athena Diagnostics Inc., Worcester, MA, USA). The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the local ethical board "Kantonale Ethikkommission Zürich" (KEK; EK-1178). All patients provided written informed consent.

Study Procedure

Participants were invited to the outpatient clinic at the Division of Nephrology (University Hospital Zurich). At the study visit the medical history was obtained, including medication and complications related to ADPKD. Blood pressure was measured in duplicate at each arm after 5 minutes of rest in sitting position using an oscillometric blood pressure device (Boso-Medicus, Jungingen, Germany). Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg or antihypertensive treatment. A fasting spot urine sample was collected after voiding the first urine of the day to measure creatinine beside the potential biomarkers. Blood samples were centrifuged and aliquoted, according to a standardized process, to obtain serum. Serum and spot urine aliquots were stored at –80°C before analysis.

Laboratory Analysis

At study visit, measurements of serum creatinine with the use of the modified Jaffé method traceable to an isotope-dilution mass spectroscopy reference were performed. Estimated GFR was calculated by applying the CKD-EPI equation.[21] NGAL (BioPorto Diagnostics A/S, Hellerup, Denmark) and KIM-1 (R&D Systems Inc., Abingdon, UK) were analyzed using commercially available Enzyme-linked Immunosorbent Assays (ELISA) according to manufacturers protocol. UMOD was analyzed by a well established ELISA based on a sheep anti-human uromodulin antibody (K90071C; Meridian Life Science, Memphis, TN) as the capture antibody, a mouse monoclonal anti-human Tamm–Horsfall protein antibody (CL 1032A; Cedarlane Laboratories, Burlington, NC) as the primary antibody, and a goat anti-mouse IgG (H+L) horseradish peroxidase–conjugated protein (172.1011; Bio-Rad Laboratories, Inc., Hercules, CA) as a secondary antibody. Human uromodulin (AG 733, stock solution: 100 μg/ml; EMD Millipore, Temecula, CA) was used to establish the standard curve. [22] CC16 was analyzed using a Latex Immuno Assay (LIA) with a continuous flow method and an assayable concentration of CC16 between 0.3 and 40 µg/L.[23] Albuminuria was assessed using Synchron Systems for Microalbumin (Beckman Coulter Inc., Brea, California, USA). The urinary albumin to creatinine ratio (UACR) was calculated as follows: Albumin (mg/dl) x 1/creatinine (mg/dl) x 1000 µg/mg. The analysis of urine osmolality was performed by cryoscopy using a freezing point depression Advanced® 2020-BIO Multi-Sample Osmometer (Advanced Instruments Inc., Norwood, Massachusetts, USA). All samples were analysed in duplicate.

Magnetic Resonance Imaging

Patients underwent kidney imaging without contrast media according to a standardized imaging protocol. The imaging was performed using a Signa Excite HDx

system (GE Healthcare, Waukesha, WI, USA) and signal perception was obtained using an eight-channel antero-posterior-phased array surface coil. Trans-axial sequences consisted of two breathhold T1-weighted fast-spoiled gradient echo sequences with 3 and 4 mm slice thicknesses. Additionally, a trans-axial T2-weighted fast spin echo sequence with respiratory triggering was performed with 3 mm slice thickness. Right and left kidney volumes were measured and calculated using the workstation Advantage Windows workstation (4.4 GE Healthcare, Buc, France). Total kidney volume (TKV) was calculated by adding the left and right kidney volume. Measurements of renal volume were done in a blinded way by two trained and independent observers. The renal hilum and the vessels were excluded from renal volume calculation. Variability was calculated as concordance correlation coefficients (95% CI) and were 1.000 (0.999–1.000) for intraobserver and 0.996 (0.995 – 0.999) for interobserver correlations.[24]

Statistical Analysis

The statistic program SAS 9.4 was used for data analysis. A plausibility check of the data preceded the statistical analysis. Univariate methods were used to characterize study population. Values are given in means with standard deviation. TKV and height adjusted kidney volume (htTKV) are reported as median, since these parameters showed a skewed distribution. Median is reported with interquartile range, which is the difference between the values of the 25th and 75th percentiles.

Spearman's correlation coefficient, r or ρ (rho) was calculated to describe the correlation between biomarkers and eGFR and htTKV. To calculate r, reflecting the relative variance part, all values of the parameters are sorted and given a rank. The smallest value gets the rank 1 and the highest number is sorted to rank *n*.[25] A positive r indicates a concordant association, whereas a negative r stands for an opposing association.

The association of biomarkers with eGFR and htTKV was evaluated by incorporating different control variables for adjustment and following a multiple linear regression approach. A stratum specific correlation analysis was performed for binary and ordinal variables. Multiple regression analysis gives information about importance and size effect of the predictors on the response variable, and about the interaction between predictors. Multiple linear regressions specify that each predictor is linear related to the response variable through its regression coefficient b, otherwise a transformation of the predictor variables is required. Prerequisites, like the independence of predictors to each other, were evaluated and fulfilled. The model determination was done using scatterplots and correlation analysis to verify linearity between outcome variable and predictors. Subsequently the regression equation was formed. Predictors were selected according to logical considerations. Adjusted R^2 and p-value were calculated as statistic measures. R^2, the coefficient of determination, reflects the proportion response variation that is explained by the predictors.[26] Predictor variables were added sequentially to the different models. The models were compared using the Akaike information criterion (AIC). The AIC is based on the likelihood and determines which model is more likely to be correct and comes closer to the "truth".[27] The smaller the AIC value the more realistic the model is, assuming, that a robust model predicts the data well containing preferably a low number of predictors meeting the requirement for parsimony and avoiding overfitting.[28] Bootstrapping was applied to estimate the 2.5^{th} and 97.5^{th} percentile confidence intervals for each model. Our dataset was used as a pool from which 500 new datasets of the same size were randomly drawn with replacement to internally validate our model results.

Results

Demographics

Between April 2006 and April 2011 139 ADPKD patients were consecutively enrolled in the study. The mean age was 31±7 years and 85 (61%) patients were male. Hypertension was present in 82 (78%) patients, and 80 (58%) patients were receiving antihypertensive medication. Among them, 50 patients were receiving angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), 16 were receiving diuretics and 14 were treated with calcium antagonists. The mean eGFR was 93±19 ml per min per 1.73 m^2 and 74 (53%) of the patients had an eGFR greater than 90 ml per min per 1.73 m^2. The median TKV was 860 cm^3 (IQR, 568 to 1191 cm^3) and 52 (37%) patients had a TKV greater than 1000 cm^3. The median htTKV was 455 cm^3 (IQR, 17 to 669 cm^3). The mean body mass index (BMI) was 24±4 kg per m^2, 5 (4%) patients had a BMI lower than 18.5 kg per m^2 and 53 (38%) patients a BMI above 25 kg per m^2 (Table 2).

Analysis of biomarker

The results of the urinary parameters: osmolality, NGAL, KIM-1, UMOD, UACR and CC16 were tabulated for the complete cohort and for the eGFR and TKV strata (Table 3). Osmolality was measured in 139 spot urine samples and other parameters were measured in 132 samples. The median osmolality was 364 mosmol per kg H_2O (IQR, 257 to 533 mosmol per kg H_2O). The median NGAL value was 9.8 µg per g creatinine (IQR, 5.3 to 23.7 µg per g creatinine) 274.6 ng per g creatinine (IQR, 131.3 to 457.3 ng per g creatinine) for Kim-1, and 16.3 mg per g creatinine (IQR, 10.2 to 26.7 mg per g creatinine). In the whole cohort, UACR was 14.0 mg per g creatinine (IQR, 8.4 to 23.1 mg per g creatinine) and the median for CC16 was 2.78 µg per l per g creatinine (IQR, 2.0 to 6.2 µg per l per g creatinine). The median of KIM-1 was higher among patients with a total kidney volume above 1000 cm^3 than among

patients with a TKV lower or equal 1000 cm^3. Osmolality, NGAL, UMOD, UACR and CC16 were similar among patients with an eGFR above 90 ml per min per 1.73m^2 and less or equal 90 ml per min per 1.73m^2.

Correlation of biomarker with indices of disease progression

Table 4 shows the correlation of biomarker with eGFR and TKV. Estimated GFR was negatively correlated with TKV (r = -0.44508, p<0.05), htTKV (r = 0.45531, p<0.05), age (r = -0.51026, p<0.05) and UACR (r = -0.20042, p<0.05). TKV was negatively correlated with eGFR (r = -0.44508, p<0.05) and UMOD (r = -0.22493, p<0.05) and positively correlated with age (r = 0.22493, p<0.05), urinary albumin (r = 0.25524, p<0.05), osmolality (r = 0.1949, p<0.05) and KIM-1 (r = 0.32129, p<0.05) (Table 4). Figure 1 and 2 show the biomarker distribution to TKV and eGFR.

Regression analysis for htTKV and eGFR as outcome parameter

Simple and multiple linear regression analysis was applied to delineate the independent associations of urinary biomarker with eGFR and htTKV. Kidney volume is affected by a number of *a priori* known biological factors, e.g. age, gender, and glomerular filtration rate. Predictive variables were chosen in a step-wise approach: In model 1 (Table 5) eGFR (β = -0.45968, p<.0001) was selected as a predictor; the term eGFR captures race, age and gender. The prognostic power of eGFR to predict htTKV is 20.6% (R^2 = 0.2055) with an AIC of -199.6. Bootstrapping revealed a percentile confidence interval of 0.0987 and 0.3374.

The selection of osmolality and UACR to the model 1 as independent variables increased the R^2 to 0.3373 (percentile CI, 0.2306 – 0.4755), and the AIC to -210.7 (Table 6; Model 2). An increase of the UACR (b = 0.20465, p<.0001) and urine osmolality (b = 0.32114, p<.0001) is independently of renal function, race, age, and gender associated with an increase in htTKV. All predictors of the model 2 are independently predictors of htTKV at

an alpha level of 0.1%. Estimated GFR has the most predictive power of all 3 variables in this model (β = -0.42435). The standardized estimate β was calculated to evaluate the predictors independently of their transformation and their level of measurement.

Adjusted R^2 of model 3 was 0.3366 after selection of KIM-1, NGAL, UMOD, CC16 to eGFR, osmolality and UACR (Table 7). A percentile confidence interval of 0.2866 to 0.5278 was obtained in bootstrap validation. Out of these seven variables, eGFR, osmolality, UACR and KIM-1 are major factors in predicting htTKV. In model 3, the variable UACR is the second largest predictor variable with a β of 0.30403. Osmolality had a β of 0.21408, and KIM-1 a β of 0.18993. NGAL, UMOD and CC16 had low β-values and were minor determinants in the prognosis of htTKV. In model 3 osmolality, UACR and KIM-1 are positively correlated with kidney volume. The AIC of model 3 was -209.9. The additional selection of Kim-1, NGAL, UMOD and CC16 did not increase R^2 and did not change AIC.

Subsequently different models were established to predict eGFR. In model 1 (Table 8) htTKV and osmolality were added on *priory* knowledge to predict eGFR. Both variables were independently associated with eGFR, and htTKV (β = -0.49803) had a larger association compared with osmolality (β = 0.22936). The adjusted R^2 for this model is 0.2515 (percentile CI, 0.1588 – 0.3809) and thus approximately 25% of eGFR variation is explained by htTKV and osmolality.

In model 2 (Table 9) the predictor parameters, htTKV, osmolality and UACR account for 22.09% of eGFR variation with an adjusted R^2 of 0.2209. A percentile confidence interval of 0.1319 to 0.3738 was obtained in bootstrap validation. The predictor htTKV has the largest impact on the outcome in this model (β = -0.48736) and osmolality showed the second largest value for standardized estimate (β = 0.21857). UACR has a comparably low β.

In model 3 (Table 10) the parameters htTKV, osmolality, UACR, NGAL, KIM-1, UMOD and CC16 entered the model. Height adjusted total kidney volume (β = -0.4726;

p<.0001) and osmolality (β = -0.27024; p = 0.006) were independently associated with changes of eGFR. The additional selection of NGAL, KIM-1, UMOD and CC16 resulted in a stable R^2 and AIC. Bootstrapping revealed a percentile confidence interval of 0.1674 to 0.4153.

Discussion

The cystogenesis in ADPKD replaces functional renal parenchyma and leads to a loss of kidney function during patients' lifespan. Since GFR, a traditional parameter of renal function, is not accurately able to assess disease state in the early disease course, the interest in establishing urinary biomarker for ADPKD has increased. In this cross-sectional study, we investigated potential biomarker at a single time point in spot urine samples of 139 ADPKD patients with preserved renal function. We demonstrated that urinary KIM-1, urinary osmolality and UACR are independently associated with kidney volume in a cohort of young ADPKD patients.

Under physiological conditions KIM-1 is only fractional expressed and an increase in urinary KIM-1 reflects tubular damage in the proximal S3 segment as shown in acute and chronic kidney injury.[29] KIM-1 has been identified as novel ciliary molecule and may interact with the PKD2 protein Transient Receptor Potential Polycystic 2 and could be involved in cellular response to changes in extracellular fluid flow detected by the cilium.[30] Furthermore expression of KIM-1 was found in murine polycystic kidneys but not in wild type mice, driving the hypothesis that ADPKD patients may display higher urinary KIM-1 excretion.[29] Urinary KIM-1 levels in ADPKD patients have been reported by Meijer et al showing increased KIM-1 levels in 24h urine samples of ADPKD compared with healthy volunteers. They identified an association of KIM-1 levels with total kidney volume, adjusted for age, gender and albuminuria. In our study, KIM-1, among the other marker of interest, showed the

strongest correlation with TKV. Multiple regression analysis revealed an independent correlation of KIM-1 with kidney volume, after adjustment for eGFR, osmolality, UACR, NGAL, UMOD, and CC16. In contrast KIM-1 was not associated with renal function when applying multiple regression analysis adjusting for renal volume, osmolality, UACR, NGAL, KIM-1, UMOD, and CC16.

Additionally to KIM-1, our study showed that urinary osmolality is reliably and independently associated with kidney volume and kidney function after adjusting for various possible confounders. ADPKD patients are known to have a defect in osmoregulation, which may be attributed to an alteration in ADH release from the pituitary glands.[31] An impaired urine concentration capacity can be observed even in children.[32] With our study we confirm and extend the knowledge about the independent association of osmolality and TKV as shown by Ho et al.[31] Hence, the assessment of osmolality in clinical practice, will add further information for disease state assessment in ADPKD patients at early disease stage.

Furthermore our results show that urinary albumin creatinine ratio independently predicts htTKV in ADPKD after multiple adjusting. Albuminuria has long been known as marker for kidney damage and is routinely assessed in the diagnosis of renal injury. UACR is independently associated with renal and cardiovascular disease. In our study urinary albumin excretion predicts the variation in htTKV but did not qualify as predictor for kidney function, expressed as eGFR. Our results confirm and extend former studies reporting a positive correlation of albumin excretion and total kidney volume.[24]

KIM-1, urine osmolality and albuminuria are independently associated with ADPKD disease state whereas we were not able to associate NGAL, UMOD and CC16 with kidney volume and function at early ADPKD state. Although these markers have been extensively

studied as biomarker in acute kidney injury, only limited data is available reporting NGAL levels in ADPKD.[7-11] Boligano et al reported markedly increased urinary NGAL levels in ADPKD patients at late disease state (eGFR 59 ± 38 ml per minute, Cockcroft-Gault formula) compared with healthy volunteers.[33] It seems that NGAL levels increase only at late disease state and thus NGAL is not suitable to predict outcome at early stage when renal function is maintained. UMOD and CC16 levels have so far not been reported in ADPKD. In our study, no association of UMOD with renal function and kidney volume was observed. Decreasing levels of urinary UMOD, which is the most abundant protein in human urine, have been reported in various settings of CKD.[12-15] Since the absolute values for urinary UMOD in our cohort are comparable with the ones reported in various cohorts, one could speculate that UMOD excretion decline starts in later stage of ADPKD and UMOD would qualifying as marker for late disease course.[34 35]

Furthermore, no association of CC16 with renal function and kidney volume was observed, suggesting that proximal tubular reabsorption is not impaired among ADPKD patients at early disease state. CC16 is secreted by bronchial Clara cells and, after filtration, reabsorbed by receptor-mediated endocytosis in the early segments of the proximal tubule.[17] Hence, all disorders associated with defective proximal tubule endocytosis lead to the urinary loss of CC16. [36] The dissociation of CC16 from Kim-1 probably reflects the functional segmentation of the proximal tubule, with endocytosis being particularly active in the S1-S2 segments whereas secretory pathways take place in the S3 segment.[37]

Our study has to be interpreted in the context of the study setting. We investigated potential biomarker and outcome in ADPKD following a cross-sectional approach. Biomarkers should be easily assessable from samples in a facile non-invasive way. The utilization of spot urine samples is ideal for this application. We enrolled a relatively high

number of participants at early disease course presenting preserved renal function. We report independent association between biomarker and outcome, but are not able to draw conclusions in respect to causal relationship. We cannot state if renal function and kidney volume follows the increase or decrease in biomarkers or if the urinary biomarker excretion causes change in renal function and kidney volume. Our results are based on a single centre in the absence of comparative groups of healthy volunteers and of patients with chronic kidney disease others than ADPKD and thus we cannot assess the specificity of our findings for ADPKD. Internal validation was performed by bootstrapping method to account for the limitation of studying the biomarkers in a single cohort without external validation data set. Our predictive models were established applying adjustment for multiple confounders. Still, multiple adjustments are not able to fully eliminate the potential for bias and confounding is likely to persist.

In conclusion, our results show that osmolality is an independent predictor for kidney volume and kidney function after adjusting for various possible confounders. The assessment of osmolality in clinics, will add additional information for disease state assessment and will precise the prognosis in ADPKD patients. Furthermore, our data shows that UACR and KIM-1 predict kidney volume independently of renal function. In our study, we followed a robust and reliable statistical approach to investigate the diagnostic properties of different urinary biomarker in a large cohort of ADPKD patients in early disease stage. Osmolality, UACR and KIM-1 have the property to assess disease state at early ADPKD disease course.

Disclosure

The authors declare no conflict of interest.

Acknowledgements

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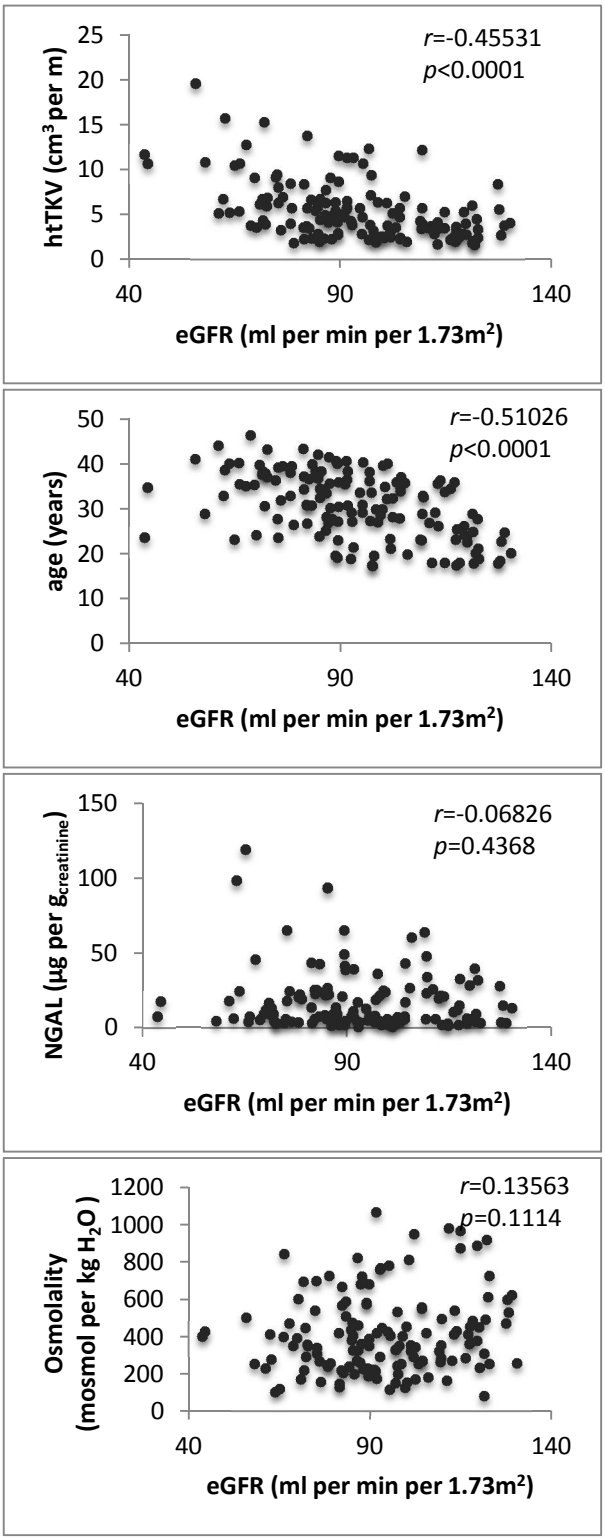
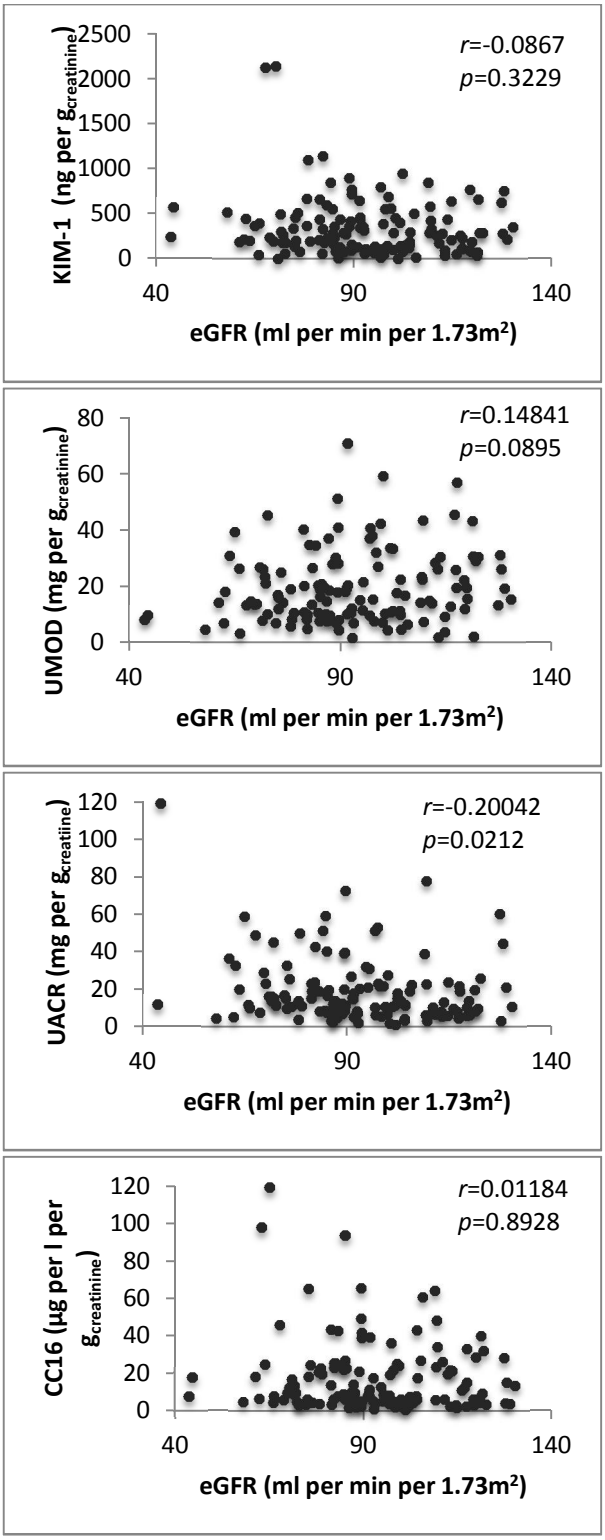
Figures

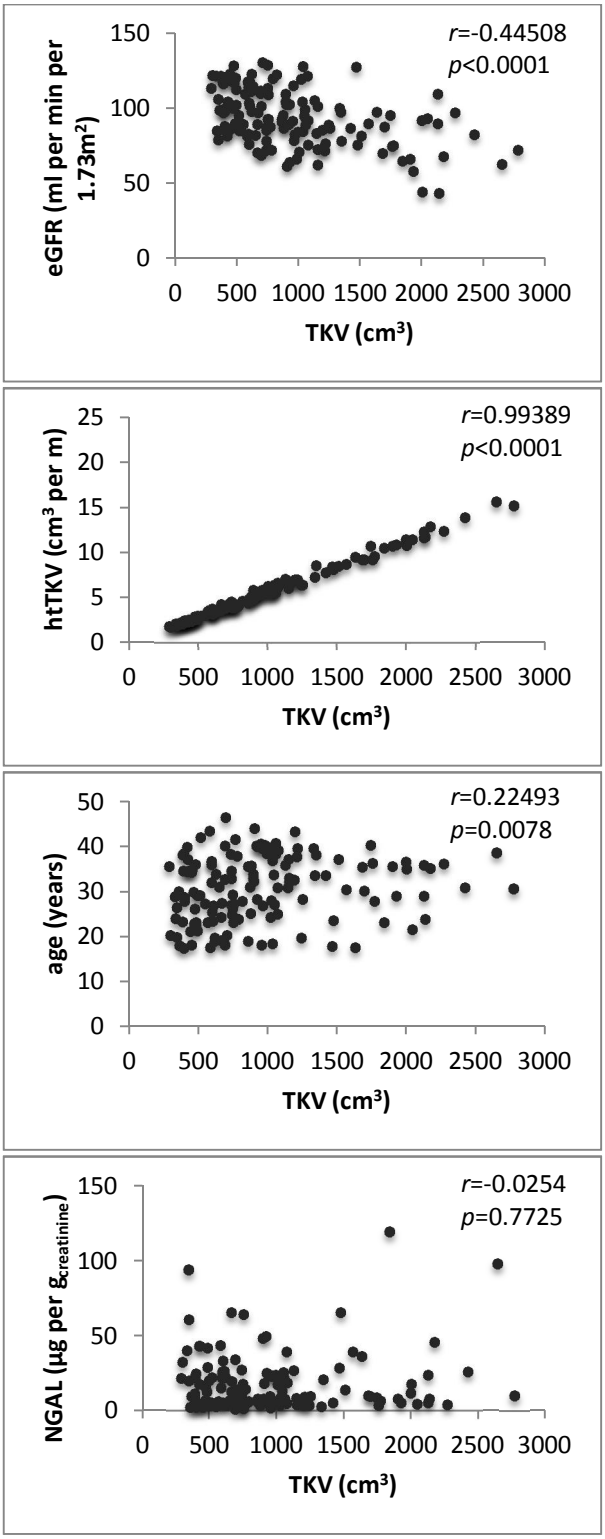
Figure 1: Estimated glomerular filtration rate (eGFR) and parameter distribution

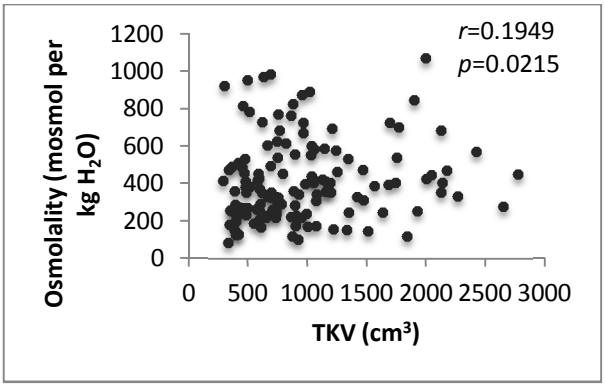


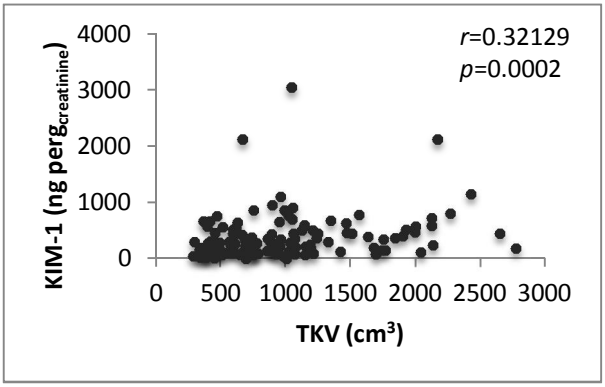


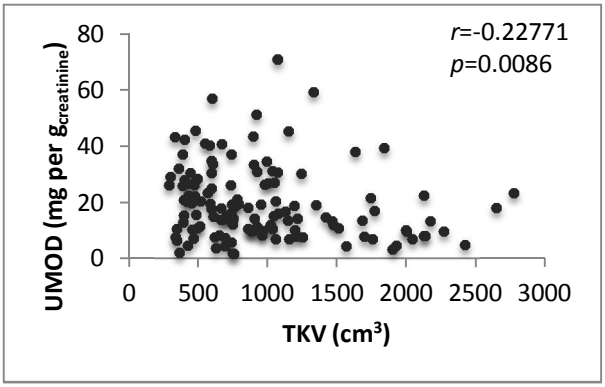
Abbreviations: htTKV –height adjusted kidney volume, NGAL – Neutrophil Gelatinase Associated Lipocalin, KIM-1 – Kidney Injury Molecule 1, UMOD –Uromodulin, UACR – Urinary Albumin-Creatinine-Ratio, CC16 – Clara Cell Protein 16

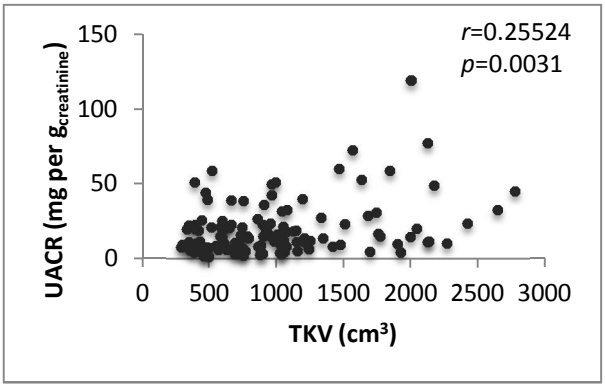
Figure 2: Total kidney volume (TKV) and parameter distribution

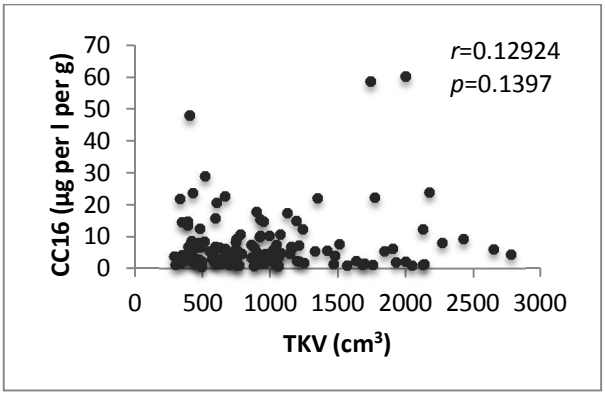



Osmolality (mosmol per kg H_2O)
1200
1000
800
600
400
200
0
0 500 1000 1500 2000 2500 3000
TKV (cm^3)
r=0.1949
p=0.0215


KIM-1 (ng per $g_{creatinine}$)
4000
3000
2000
1000
0
0 500 1000 1500 2000 2500 3000
TKV (cm^3)
r=0.32129
p=0.0002


UMOD (mg per $g_{creatinine}$)
80
60
40
20
0
0 500 1000 1500 2000 2500 3000
TKV (cm^3)
r=-0.22771
p=0.0086


UACR (mg per $g_{creatinine}$)
150
100
50
0
0 500 1000 1500 2000 2500 3000
TKV (cm^3)
r=0.25524
p=0.0031



Abbreviations: eGFR – estimated glomerular filtration rate, htTKV –height adjusted kidney volume, NGAL – Neutrophil Gelatinase Associated Lipocalin, KIM-1 – Kidney Injury Molecule 1, UMOD – Uromodulin, UACR – Urinary Albumin-Creatinine-Ratio, CC16 – Clara Cell Protein 16

Tables

Table 1: Eligibility criteria[19]

- Age ≥ 18
- GFR ≥ 70 ml/min/1.73m^2 (Cockcroft-Gault formula)
- Clinical diagnosis of ADPKD based on kidney imaging (modified Ravine criteria) and family history
  - Positive family history for ADPKD
    - patients < 30 years: ≥ 2 cysts in either kidney
    - patients ≥ 30 years: ≥ 2 cysts in each kidney
  - Negative family history for ADPKD cystic kidney disease by sonography: proof of a mutation in the PKD1 or PKD2 gene
- Patient provided written informed consent

Table 2: Characteristics of study cohort

	ADPKD n = 139
Age – years	31±7
Sex – no. (%)	
Female	54 (39)
Male	85 (61)
Body mass index - kg per m^2	24±4
BMI <18.5	5 (4)
BMI 18.5 – 25	81 (58)
BMI >25	53 (38)
eGFR – ml per min per $1.73m^2$	93±19
CKD stage 1	74 (53)
CKD stage 2	61 (44)
CKD stage 3	4 (3)
TKV – cm^3	860 (568 to 1191)
htTKV – cm^3 per m	455 (317 to 669)
Hypertension – no. (%)*	
Yes	82 (78)
No	23 (22)
Blood pressure – mmHg	
Systolic	131±16
Diastolic	83±11
Antihypertensive Medication - no. (%)	
ACE / ARB	50 (36)
Calcium antagonist	14 (10)
Diuretics	16 (12)

Abbreviations: eGFR – estimated glomerular filtration rate. TKV – total kidney volume, htTKV – height adjusted kidney volume, ACE – angiontensin converting enzyme, ARB – angiotensin II receptor blocker. Values are means ± standard deviation and numbers (percentage), TKV and htTKV are reported as median (interquartile range), *total number of observations =

Table 3: Biomarker Analysis

	n	Complete Cohort	eGFR >90 ml per min per 1.73m²	eGFR ≤90 ml per min per 1.73m²	TKV ≤1000 cm³	TKV >1000 cm³
Osmolality – mosmol per kg H_2O	139	364 (257 to 533)	377 (266 to 534)	360 (243 to 506)	330 (236 to 497)	417 (332 to 547)
NGAL – µg per $g_{creatinine}$	132	9.8 (5.3 to 23.7)	8.7 (4.7 to 22.8)	11.3 (5.8 to 24.3)	12.5 (5.3 to 24.3)	9.0 (5.3 to 21.3)
KIM-1 – ng per $g_{creatinine}$	132	274.6 (131.3 to 457.3)	272.0 (113.9 to 448.8)	274.6 (161.3 to 479.9)	211.6 (106.4 to 362.5)	391.3 (196.1 to 581.0)*
UMOD – mg per $g_{creatinine}$	132	16.3 (10.2 to 26.7)	18.1 (10.9 to 29.8)	14.8 (9.1 to 25.6)	19.4 (10.7 to 28.5)	13.6 (8.3 to 21.6)
UACR – mg per $g_{creatinine}$	132	14.0 (8.4 to 23.1)	11.6 (6.9 to 21.8)	15.4 (9.9 to 27.2)	12.0 (7.7 to 21.3)	15.2 (10.4 to 31.1)
CC16 – µg per l per $g_{creatinine}$	132	2.8 (2.0 to 6.2)	3.0 (2.0 to 5.9)	2.6 (2.0 to 6.2)	2.6 (2.0 to 4.8)	3.2 (1.7 to 8.9)

Abbreviations: NGAL – Neutrophil Gelatinase Associated Lipocalin, KIM-1 – Kidney Injury Molecule 1, UMOD – Uromodulin, UACR – Urinary Albumin-Creatinine-Ratio, CC16 – Clara Cell Protein 16. Values are reported as median (interquartile range), * $p < 0.05$

Table 4: Spearman Correlation Coefficient *r*

	eGFR	TKV	htTKV	Age	NGAL	OSMOL	KIM-1	UMOD	UACR	CC16
eGFR	1	-0.44508*	-0.45531*	-0.51026*	-0.06826	0.13563	-0.0867	0.14841	-0.20042*	0.01184
TKV	-0.44508*	1	0.99389*	0.22493*	-0.0254	0.1949*	0.32129*	-0.22771*	0.25524*	0.12924

Abbreviations: eGFR – estimated glomerular filtration rate, TKV – total kidney volume, htTKV –height adjusted kidney volume, NGAL – Neutrophil Gelatinase Associated Lipocalin, OSMOL – Osmolality, UMOD –Uromodulin, KIM-1 –Kidney Injury Molecule 1, UACR – Urinary Albumin-Creatinine-Ratio, CC16 – Clara Cell Protein 16. * $p < 0.05$

Table 5: Simple linear regression height adjusted total kidney volume (transformed to log htTKV)

Model 1

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	2.20103	<.0001	0	0.1145	0.2055	-199.6
eGFR[1] – ml per min per 1.73m²	-0.00007127	<.0001	-0.45968	0.000011 81		

[1]square root transformed

Table 6: Multiple linear regression height adjusted total kidney volume (transformed to log htTKV)

Model 2

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	-0.29424	0.5704	0	0.51711	0.3373	-210.7
eGFR[1] – ml per min per 1.73m^2	-0.00006612	<.0001	-0.42435	0.00001149		
Osmolality[2] – mosmol per kg H_2O	0.32114	<.0001	0.30774	0.07825		
UACR[2] – mg per $g_{creatinine}$	0.20465	<.0001	0.31058	0.04985		

[1] square root transformed
[2] log transformed

Table 7: Multiple linear regression height adjusted total kidney volume (transformed to log htTKV)

Model 3

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	0.00847	0.9895	0	0.64145	0.3366	-209.9
eGFR[1] – ml per min per1.73m^2	-0.00006259	<.0001	-0.40173	0.00001166		
Osmolality[2] – mosmol per kg H_2O	0.2234	0.0186	0.21408	0.09366		
UACR[2] – mg per $g_{creatinine}$	0.20033	0.001	0.30403	0.05951		
KIM-1[2] – ng per $g_{creatinine}$	0.09432	0.0191	0.18993	0.0475		
NGAL[2] – µg per $g_{creatinine}$	-0.05253	0.2709	-0.09574	0.0397		
UMOD[2] – mg per $g_{creatinine}$	-0.04606	0.4653	-0.06085	0.06289		
CC16[2] – µg per l per $g_{creatinine}$	-0.00504	0.9212	-0.00794	0.05087		

[1] square root transformed
[2] log transformed

Table 8: Multiple linear regression estimated glomerular filtration rate (square root transformed eGFR) Model 1

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	4899.70827	0.1014	0	2970.99215	0.2515	2214.2
htTKV[1] – cm^3 per m	-3212.08387	<.0001	-0.49803	483.52856		
Osmolality[1] – mosmol per kg H_2O	1549.70316	0.0027	0.22936	506.54097		

[1] log transformed

Table 9: Multiple linear regression estimated glomerular filtration rate (transformed to square root eGFR) Model 2

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	4899.8604	0.1681	0	3534.68607	0.2209	2104.
htTKV[1] – cm^3 per m	-3127.98641	<.0001	-0.48736	543.58333		3
Osmolality[1] – mosmol per kg	1463.87536	0.0098	0.21857	557.90345		
H_2O UACR[1] – mg per $g_{creatinine}$	100.97551	0.7824	0.02388	364.80352		

[1] log transformed

Table 10: Multiple lineare regression estimated glomerular filtration rate (transformed to square root eGFR) Model 3

variable	Parameter estimate b	*p*	Standardized estimate β	Standard Error	Adjusted R^2	AIC
Intercept	170.01158	0.9697	0	4465.37589	0.2195	2108.4
htTKV[1] – cm^3 per m	-3333.33092	<.0001	-0.47261	564.97273		
Osmolality[1] – mosmol per kg	1809.95369	0.006	0.27024	646.61622		
H_2O	42.27981	0.9224	0.01	432.9461		
UACR[1] – mg per $g_{creatinine}$	-136.7632	0.6812	-0.03884	332.06115		
NGAL[1] – µg per $g_{creatinine}$	185.45311	0.5123	0.05818	282.16858		
KIM-1[1] – ng per $g_{creatinine}$	798.52678	0.0675	0.16434	432.84451		
UMOD[1] – mg per $g_{creatinine}$	-138.45145	0.6963	-0.03397	353.90411		
CC16[1] – µg per l per $g_{creatinine}$						

[1] log transformed

Appendix II:

Chancen und Herausforderungen von Tolvaptan zur Behandlung von ADPKD ï Ein aktueller Stand der Entwicklung

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Einführung

Tolvaptan (Samsca®) fördert die renale Ausscheidung von freiem Wasser und wird deshalb als Aquaretikum bezeichnet. Die chemische Strukur von Tolvaptan besteht aus einem C26H25ClN2O3 Molekül und ordnet sich in die neue Arzneimittelklasse genannt Vaptan und Aquaretika ein. Das first-in-class Medikament blockiert selektiv den Vasopressin-2 (V2) Rezeptor im distalen Sammelrohr und hebt somit die physiologische Wirkung von Vasopressin (Synonym Antidiuretisches Hormon (ADH)) auf. Die Aktivierung des V2-Rezeptors durch Vasopressin führt über cyclischem Adenosinmonophosphat (cAMP) zur vermehrten Translation von Aquaporinen, welche die Tubuluszellen wasserdurchlässig machen. Tolvaptan verhindert diesen Prozess und somit bleiben die Tubuluszellen für Wasser undurchlässig und die Rückresorption von Wasser aus dem Primärharn in das Blut wird verhindert. Es kommt entsprechend zu einer starken Polyurie, insbesondere bei normaler Nierenfunktion. Im Gegensatz zu einem konventionellen Diuretika, verursacht Tolvaptan keinen Elekrolytverlust. Tolvaptan ist zur Behandlung von kardial bedingten Ödemen und des Syndroms der inadäquaten ADH Sekretion (SIADH) von der European Medicines Agency (EMA) und der Food and Drug Administration (FDA) zugelassen [1]. Ein Zulassungsantrag an die Swissmedic für diese beiden Indikationen wurde bisher nicht gestellt.

Die autosomal-dominante polyzystische Nierenerkrankung (Englisch autosomal dominant polycystic kidney disease) ist eine monogene vererbbare Erkrankung, welche durch die Entwicklung von einer Vielzahl von Zysten in beiden Nieren gekennzeichnet ist. Häufig werden betroffene Patienten zwischen dem 50. und 60. Lebensjahr nierenersatzpflichtig. ADPKD Patienten zeigen bereits in frühen Stadien eine eingeschränkte Urinkonzentrationsfähigkeit der Niere mit begleitend erhöhten Vasopressinspiegeln [1]. Vasopressin erhöht die Konzentration von cAMP, welches pro-proliferative Signalwege und

die chloridabhängige Flüssigkeitssekretion in die Zysten stimuliert. Der verstärkten Aktivierung des V2-Rezeptors bei ADPKD wird somit eine kausale Rolle in der Krankheitsprogression zugeschrieben.

Studienresultate

Die Therapieeffizienz von Tolvaptan zur Behandlung von ADPKD wurde in einer multizentrischen doppelblinden Placebo kontrollierten Phase III-Studie (TEMPO 3:4) geprüft, in welcher 1445 ADPKD Patienten im Alter von 18 bis 50 Jahren eingeschlossen wurden. Der primäre Endpunkt war das prozentuale Nierenwachstum und als kombinierter sekundärer Endpunkt: die Verschlechterung der geschätzten glomerulären Filtrationsrate, der Albuminurie, der Hypertonie, sowie der Inzidenz von behandlungsbedürftigen Nierenschmerzen. Über einen Beobachtungszeitraum von 3 Jahren zeigten die Ergebnisse der Studie eine Zunahme des Nierenvolumens von 2,8% pro Jahr in der Tolvaptangruppe verglichen zu der Placebogruppe von 5,5% pro Jahr. Tolvaptan senkte somit die Wachstumsrate des Nierenvolumens um 2,7 % pro Jahr (95%CI von -3.3 bis -2.1). Zudem wurde der Nierenfunktionsverlust in der Tolvaptangruppe, im Vergleich zur Placebogruppe, vermindert. Weiterhin konnte in der Tolvaptangruppe ein schützender Effekt der ADPKD-assoziierten Komplikationen, wie Nierenschmerzen, Infektion der Harnwege und Blut im Urin (Hazard ratio: 0.87; 95% CI, 0.78 - 0.97) aufgezeigt werden [2].

Als unerwünschte Nebenwirkungen, die auf den Wirkmechanismus von Tolvaptan zurückzuführen sind, wurde eine Polyurie in der Tolvaptan Gruppe von 38,3% versus 17,2% in der Placebo Gruppe beobachtet. Als weitere gehäufte unerwünschte Nebenwirkungen in der Tolvaptan Gruppe wurde Pollakisurie (23,2 % versus 5,4%), Nykturie (29,1% versus 13,0%) und Durst (55,3% versus 20,5%) berichtet. Überaschenderweise zeigte sich in der Tolvaptangruppe eine Häufung von Leberenzymerhöhungen (0,9% und 0,4% Inzidenz in der

Tolvaptan- und der Placebo-Gruppe), wovon 4,7% klinisch bedeutsam waren und vorwiegend in den ersten 18 Studienmonaten auftraten. In der Studie wurden drei Hy's Law (zwei während des Behandlungzeitraum) identifiziert, jedoch ist es bei diesen Fällen zu keinem lebensbedrohlichem Ereignis gekommen (Leberversagen, Transplantation oder Tod). Für die Identifikation eines Hy's Law Case in einer klinischen Studie müssen die drei nachfolgenden Kriterien zutreffen: ein erhöhter Aminotransferasewert von >3xULN, eine akalische Phosphatase (ALP < 2x ULN), sowie ein erhöhter Gesamtbilirubinwert von > 2x ULN.

Die Feststellung von zwei oder mehr Hy's Law in einer klinischen Studie ist ein starker Indikator für eine mögliche medikamenten-induzierte Leberschädigung (Englisch drug-induced liver injury, DILI).

In der vorliegenden Studie scheint ein Anstieg der Alanin-Aminotransferase (ALT) öfters bei der Behandlung mit Tolvaptan vorzukommen. Diese Tolvaptan-assoziierte Leberenzymerhöhung wurde in vorgehenden klinischen Studien nicht beobachtet. In Nachfolgestudien und klinischer Anwendung ist daher ein enges Monitoring der Leberwerte erforderlich.

Stellenwert einer Tolvaptan Therapie auf die Kosten-Effektivität

Die Kosten-Effektivität einer Tolvaptantherapie bis zur Notwendigkeit eines Nierenersatzverfahrens wurde in einem gesundheitsökonomischen Markov-Model analysiert. Das Ziel der Studie war die Berechnung eines qualitäts-adjustierten Lebensjahr (QALY) der Tolvaptan Therapie auf unterschiedliche ADPKD Populationen. Die Ergebnisse zeigen, dass eine Therapie (bei Patienten ab 40 Jahren und einer geschätzten glomerulären Filtrationsrate von 80 ml/min/1,73 m²) im Vergleich zur keiner Therapie, die mediane Zeit bis zur Notwendigkeit eines Nierenersatzverfahrens auf 6,5 Jahre herauszögert und die

Lebenserwartung sich durchschnittlich um 2,6 Jahre erhöht. Ausgehend von dem aktuellen Handelspreis (montl. pro Patient 5.760 $) müssten um ein QALY durch die Tolvaptan Therapie zu gewinnen, nahezu 750.000 $ pro Jahr investiert werden. Die Studie zeigt auf, dass eine Zulassung von Tolvaptan für die Therapie von ADPKD zum derzeitigen Handelspreis mit sehr hohen Kosten verbunden wäre [3]. Allerdings ist zu erwarten, dass bei einer Zulassung von Tolvaptan zur Behandlung von ADPKD das Preisniveau angepasst wird, da es sich um eine lebenslange Therapie handelt. Die momentane Preisgestaltung wurde für die Indikation bei einer Kurzeittherapie des Syndroms der inadäquaten ADH-Sekretion (SIADH) festgelegt.

Aktuelle Entwicklung & Ausblick

Auf Grund von umfassenden Analysen von Krankenversicherungsdaten wurde ADPKD durch die FDA der Status „Orphan Disease“ vergeben. Die FDA hat sich im August 2013 gegen die Zulassung von Tolvaptan für ADPKD ausgesprochen und weitere Daten und Analysen vom Otsuka, dem Produzenten von Tolvaptan, sowie ein günstigeres Nutzen-Risiko-Verhältnis gefordert [4]. Ende Dezember 2013 wurde der Zulassungsantrag für Tolvaptan in der Indikation ADPKD an die EMA übermittelt. Der EMA Entscheid wird in einem Jahr erwartet. In Japan wird derzeit ebenfalls die Zulassung für Tolvaptan als Therapie für ADPKD geprüft und für das zweite Quartal 2014 ist die Freigabe geplant [5]. Otsuka Schweiz hat das Zulassungsdossier für Tolvaptan in der Indikation ADKPD im ersten Quartal 2014 bei Swissmedic eingereicht, somit ist eine mögliche Markzulassung von Tolvaptan in der Schweiz frühestens im Jahr 2015 zu erwarten. Die von der FDA geforderte Nachfolgestudie ist in der Planungsphase (Outcome: Nierenfunktion) und der Einschluss der ADPKD Patienten soll ab Juni/Juli 2014 erfolgen. Die Studiendauer beträgt ein Jahr und circa 1000 ADPKD sollen weltweit eingeschlossen werden.

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